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Screening for prostate cancer (Review)

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Screening for prostate cancer.
Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD004720.
DOI: 10.1002/14651858.CD004720.pub3.

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[Intervention Review]

Screening for prostate cancer

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Editorial group: Cochrane Urology Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2013.

Citation: Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. *Cochrane Database of Systematic Reviews* 2013, Issue 1. Art. No.: CD004720. DOI: 10.1002/14651858.CD004720.pub3.

ABSTRACT

Background

Any form of screening aims to reduce disease-specific and overall mortality, and to improve a person's future quality of life. Screening for prostate cancer has generated considerable debate within the medical and broader community, as demonstrated by the varying recommendations made by medical organizations and governed by national policies. To better inform individual patient decision-making and health policy decisions, we need to consider the entire body of data from randomised controlled trials (RCTs) on prostate cancer screening summarised in a systematic review. In 2006, our Cochrane review identified insufficient evidence to either support or refute the use of routine mass, selective, or opportunistic screening for prostate cancer. An update of the review in 2010 included three additional trials. Meta-analysis of the five studies included in the 2010 review concluded that screening did not significantly reduce prostate cancer-specific mortality. In the past two years, several updates to studies included in the 2010 review have been published thereby providing the rationale for this update of the 2010 systematic review.

Objectives

To determine whether screening for prostate cancer reduces prostate cancer-specific mortality or all-cause mortality and to assess its impact on quality of life and adverse events.

Search methods

An updated search of electronic databases (PROSTATE register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CANCERLIT, and the NHS EED) was performed, in addition to handsearching of specific journals and bibliographies, in an effort to identify both published and unpublished trials.

Selection criteria

All RCTs of screening versus no screening for prostate cancer were eligible for inclusion in this review.

Data collection and analysis

The original search (2006) identified 99 potentially relevant articles that were selected for full-text review. From these citations, two RCTs were identified as meeting the inclusion criteria. The search for the 2010 version of the review identified a further 106 potentially relevant articles, from which three new RCTs were included in the review. A total of 31 articles were retrieved for full-text examination based on the updated search in 2012. Updated data on three studies were included in this review. Data from the trials were independently extracted by two authors.

Main results

Five RCTs with a total of 341,342 participants were included in this review. All involved prostate-specific antigen (PSA) testing, with or without digital rectal examination (DRE), though the interval and threshold for further evaluation varied across trials. The age of participants ranged from 45 to 80 years and duration of follow-up from 7 to 20 years. Our meta-analysis of the five included studies indicated no statistically significant difference in prostate cancer-specific mortality between men randomised to the screening and control groups (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.86 to 1.17). The methodological quality of three of the studies was assessed as posing a high risk of bias. The European Randomized Study of Screening for Prostate Cancer (ERSPC) and the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial were assessed as posing a low risk of bias, but provided contradicting results. The ERSPC study reported a significant reduction in prostate cancer-specific mortality (RR 0.84, 95% CI 0.73 to 0.95), whilst the PLCO study concluded no significant benefit (RR 1.15, 95% CI 0.86 to 1.54). The ERSPC was the only study of the five included in this review that reported a significant reduction in prostate cancer-specific mortality, in a pre-specified subgroup of men aged 55 to 69 years of age. Sensitivity analysis for overall risk of bias indicated no significant difference in prostate cancer-specific mortality when referring to the meta analysis of only the ERSPC and PLCO trial data (RR 0.96, 95% CI 0.70 to 1.30). Subgroup analyses indicated that prostate cancer-specific mortality was not affected by the age at which participants were screened. Meta-analysis of four studies investigating all-cause mortality did not determine any significant differences between men randomised to screening or control (RR 1.00, 95% CI 0.96 to 1.03). A diagnosis of prostate cancer was significantly greater in men randomised to screening compared to those randomised to control (RR 1.30, 95% CI 1.02 to 1.65). Localised prostate cancer was more commonly diagnosed in men randomised to screening (RR 1.79, 95% CI 1.19 to 2.70), whilst the proportion of men diagnosed with advanced prostate cancer was significantly lower in the screening group compared to the men serving as controls (RR 0.80, 95% CI 0.73 to 0.87). Screening resulted in a range of harms that can be considered minor to major in severity and duration. Common minor harms from screening include bleeding, bruising and short-term anxiety. Common major harms include overdiagnosis and overtreatment, including infection, blood loss requiring transfusion, pneumonia, erectile dysfunction, and incontinence. Harms of screening included false-positive results for the PSA test and overdiagnosis (up to 50% in the ERSPC study). Adverse events associated with transrectal ultrasound (TRUS)-guided biopsies included infection, bleeding and pain. No deaths were attributed to any biopsy procedure. None of the studies provided detailed assessment of the effect of screening on quality of life or provided a comprehensive assessment of resource utilization associated with screening (although preliminary analyses were reported).

Authors' conclusions

Prostate cancer screening did not significantly decrease prostate cancer-specific mortality in a combined meta-analysis of five RCTs. Only one study (ERSPC) reported a 21% significant reduction of prostate cancer-specific mortality in a pre-specified subgroup of men aged 55 to 69 years. Pooled data currently demonstrates no significant reduction in prostate cancer-specific and overall mortality. Harms associated with PSA-based screening and subsequent diagnostic evaluations are frequent, and moderate in severity. Overdiagnosis and overtreatment are common and are associated with treatment-related harms. Men should be informed of this and the demonstrated adverse effects when they are deciding whether or not to undertake screening for prostate cancer. Any reduction in prostate cancer-specific mortality may take up to 10 years to accrue; therefore, men who have a life expectancy less than 10 to 15 years should be informed that screening for prostate cancer is unlikely to be beneficial. No studies examined the independent role of screening by DRE.

PLAIN LANGUAGE SUMMARY

Screening for prostate cancer

Prostate cancer is one of the most prevalent forms of cancer in men worldwide. Screening for prostate cancer implies that diagnostic tests be performed in the absence of any symptoms or indications of disease. These tests include the digital rectal examination (DRE), the prostate-specific antigen (PSA) blood test and transrectal ultrasound (TRUS) guided biopsy. Screening aims to identify cancers at an early and treatable stage, therefore increasing the chances of successful treatment while also improving a patient's future quality of life. This review identified five relevant studies, comprised of 341,342 participants in total. Two of the studies were assessed to be of low risk of bias, whilst the remaining three had more substantive methodological weaknesses. Meta-analysis of all five included studies demonstrated no statistically significant reduction in prostate cancer-specific mortality (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.86 to 1.17). Meta-analysis of the two low risk of bias studies indicated no significant reduction in prostate cancer-specific mortality (RR 0.96, 95% CI 0.70 to 1.30). Only one study included in this review (ERSPC) reported a significant 21% relative reduction (95% CI 31% to 8%) in prostate cancer-specific mortality in a pre-specified subgroup of men. These results were primarily driven by two countries within the ERSPC study that had very high prostate cancer mortality rates and unusually large reduction estimates. Among men aged 55 to 69 years in the ERSPC study, the study authors reported that 1055 men would need to be screened to prevent one additional death from prostate cancer during a median follow-up duration of 11 years. Harms included overdiagnosis and harms associated with overtreatment, including false-positive results for the PSA test, infection, bleeding, and pain associated with subsequent biopsy.

Summary of findings for the main comparison. Screening for prostate cancer

Screening for prostate cancer

Patient or population: adult male patients
Settings: primary or secondary care
Intervention: screening for prostate cancer

Outcomes[1]	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Screening				
All-cause mortality	**21 per 100**	**21 per 100** (20 to 22)	**RR 1** (0.96 to 1.03)	294856 (4 studies[2,3])	⊕⊕⊕⊖ **moderate** [4,5,6]	
Prostate cancer-specific mortality	**7 per 1000**	**7 per 1000** (6 to 8)	**RR 1** (0.86 to 1.17)	341342 (5 studies[2,3])	⊕⊕⊕⊖ **moderate** [6,7,8,9]	
Prostate cancer diagnosis	**68 per 1000**	**88 per 1000** (69 to 112)	**RR 1.3** (1.02 to 1.65)	294856 (4 studies[2,3])	⊕⊕⊖⊖ **low** [4,9,10,11]	
Tumour stage (localised T1-T2, N0, M0)	**6 per 100**	**10 per 100** (7 to 15)	**RR 1.79** (1.19 to 2.7)	247954 (3 studies[12,13])	⊕⊕⊖⊖ **low** [9,14,15,16]	
Tumour stage (advanced T3-4, N1, M1)	**11 per 1000**	**9 per 1000** (8 to 9)	**RR 0.8** (0.73 to 0.87)	247954 (3 studies[12,13])	⊕⊕⊕⊖ **moderate** [14,15,17]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Information on costs, quality of life, metastatic disease at follow up, and harms of screening was limited and could not be meta-analysed; available information is summarised in the text.

[2] ERSPC study data includes all ages (not just 'core' age group defined by trialists).
[3] PLCO study data is at 10 years of follow-up for this outcome.
[4] Risk of bias was 'high' or 'unclear' for allocation concealment in 3 studies; 'high' or 'unclear' for random sequence generation in 2 studies; 'low' for blinding in all 4 studies; 'unclear' for incomplete outcome data in 2 studies; 'unclear' for selective reporting in 1 study; and 'high' or 'unclear' for other bias in 2 studies.
[5] I^2 = 62%; Chi^2 = 7.99 (P = 0.05).
[6] Norrkoping study data for this outcome only included men who had been diagnosed with prostate cancer up to 12/31/1999, in whom mortality was then followed until 12/31/2008.
[7] Risk of bias was 'high' or 'unclear' for allocation concealment in 4 studies; 'high' or 'unclear' for random sequence generation in 3 studies; 'unclear' for blinding of outcome assessment in 1 study; 'unclear' for incomplete outcome data in 2 studies; 'unclear' for selective reporting in 2 studies; and 'high' or 'unclear' for other bias in 3 studies.
[8] I^2 = 46%; Chi^2 = 7.40 (P = 0.12).
[9] Wide 95% CI.
[10] I^2 = 98%; Chi^2 = 162.78 (P < 0.00001).
[11] Screening intervention and screening interval varied between and even within some studies; the method of diagnosis also varied.
[12] PLCO study data is provided at 13 years of follow-up for this outcome.
[13] ERSPC study data includes only 'core' age group, as defined by trialists.
[14] Risk of bias was 'high' or 'unclear' for allocation concealment in 2 studies; 'high' for random sequence generation in 1 study; 'low' for blinding in all 3 studies; 'unclear' for incomplete outcome data in 2 studies; 'low' for selective reporting in all 3 studies; and 'high' or 'unclear' for other bias in 2 studies.
[15] Tumour stage was unknown for some participants diagnosed with prostate cancer in all 3 studies.
[16] I^2 = 99%; Chi^2 = 288.85 (P < 0.00001).
[17] I^2 = 0%; Chi^2 = 1.34 (P = 0.51).

BACKGROUND

Description of the condition

Adenocarcinoma of the prostate is common, with it being the second most prevalent cancer in men worldwide and the sixth leading cause of death in men (Jemel 2011). Prostate cancer is the most commonly diagnosed cancer in developed countries and the third leading cause of death in men in those countries (Jemel 2011). It is the sixth most commonly diagnosed cancer in developing countries (Jemel 2011). Advanced age is the primary risk factor, and it is more common in black men and those with a first degree relative who has had prostate cancer (Grönberg 2003). Prostate cancer is most commonly diagnosed in ageing men, with more than 75% of all prostate cancers diagnosed in men aged 65 years and over (Parkin 2005). Prostate cancer incidence is highest in Australia, North America, Northern and Western Europe, as well as the Caribbean (Jemel 2011). Conversely, incidence rates are lowest in South-Eastern and South-Central Asia, including China (Jemel 2011). This geographic variation may be attributed to racial, dietary, and environmental factors as well as differences in the intensity of cancer detection efforts.

Prostate cancer can cause haematuria or urinary obstruction due to local progression. Cancer that spreads outside the gland may result in lower extremity oedema from regional lymphatic obstruction or pain from bone metastasis. However, the vast majority of men with prostate cancer have no symptoms and their tumours are detected by routine testing. Bothersome lower urinary tract symptoms due to benign prostatic obstruction are common in elderly men and may result in increased concentrations of prostate-specific antigen (PSA) but are not associated with an increased prostate cancer incidence (Jones 2010). For most men prostate cancer is slow growing and does not result in clinical signs or symptoms during their lifetime (Berry 1984; Holman 1999). However, in some men prostate cancer progresses and is a leading cause of cancer morbidity and mortality. Efforts to accurately determine prognosis have been problematic. However, high histologic grade, high PSA values, and larger tumour size are associated with worse disease-specific prognosis (Partin 1993).

Description of the intervention

The PSA test and digital rectal examination (DRE) are used as primary screening tools in the early detection of prostate cancer. Transrectal ultrasound (TRUS) and TRUS-guided needle biopsies are performed to confirm diagnosis following PSA or DRE testing, or both. These screening techniques aim to reduce overall and disease-specific morbidity and mortality by identifying prostate cancer more frequently and earlier, and thus they hopefully lead to early treatment regimens that may be more effective when applied to cancer confined to the prostate gland.

How the intervention might work

Screening for any type of cancer aims to increase the chances of successful treatment through early detection of the disease. Screening may be performed by one of three methods, mass (that is large scale screening of an entire population); selective (that is screening high-risk populations); or opportunistic (for example incorporated as part of a medical consultation). Testing for, or diagnosing of, a disease differs from screening. Diagnostic testing attempts to identify the disease in the presence of symptoms, whilst screening is offered to symptom-free individuals. In the case of prostate cancer screening, the presence of lower urinary tract symptoms (LUTS), typically due to benign prostatic obstruction, are very common in the ageing male and are not considered to increase prostate cancer risk (Jones 2010). Therefore, PSA testing or DRE in men with LUTS is also considered screening.

Why it is important to do this review

Prostate cancer is common and a leading cause of morbidity and mortality. Prostate cancer rarely produces reliable early warning clinical signs or symptoms while still confined to the prostate gland. Preventive strategies, such as oral 5-alpha reductase inhibitors, are not widely utilised or effective curative treatments, and do not work for disease that has spread beyond the prostate gland (Wilt 2008). Therefore, effective early detection and treatment strategies in asymptomatic men could potentially provide a large benefit to many men. While the intention of screening for prostate cancer is to decrease mortality and increase quality of life, the true benefit of screening for prostate cancer remains uncertain. Use of the DRE as a screening tool is limited due to poor reliability, sensitivity, and the inability to palpate the entire prostate gland, especially for small tumours that have not reached the prostatic capsule (Gambert 2001). However, it has the potential advantage of limiting overdiagnosis by detecting tumours that have grown in size to be detected on physical examination and that may progress to cause clinical signs or symptoms if left untreated. The PSA test produces high false-negative and false-positive results, depending on the thresholds utilised to define abnormality, and may detect prostate cancers that are unlikely to cause future health problems even if left untreated (overdiagnosis) (Gambert 2001). Recent data from a nested case-control study, which assessed the validity standards of the PSA test, concluded that the PSA test does not attain the likelihood ratios (that is the likelihood of a given test result in a person with the disease compared to the likelihood that the same result would be apparent in a person without the disease) suitable for a screening test, regardless of what cut-off value for the PSA is assigned (Holmström 2009).

Additional causes for concern include the cost of follow-up tests, the potentially invasive nature of these tests, and the subsequent use of treatment regimens that may provide additional adverse events. Although a man's risk of prostate cancer diagnosis increases with age, many men will live with undiagnosed prostate cancer only to die from another disorder, as has been confirmed in unselected autopsies (Berry 1984; Holman 1999). Screening for prostate cancer in this scenario results in overdiagnosis, thereby exposing a patient to unnecessary treatment (Draisma 2003). Additionally, the long-term prognosis for most men (especially elderly men) with PSA-detected prostate cancer is excellent, even among those treated conservatively, and is superior to that for men diagnosed prior to PSA testing. This may be due in part to additional lead time, overdiagnosis related to PSA testing, grade migration, or advances in other medical care (Lu-Yao 2009). It has been estimated that screening for prostate cancer includes a lead-time bias (that is advancing the time of diagnosis) between five to 13 years (Draisma 2003).

The uncertainty about the effectiveness of prostate cancer screening has been further highlighted by the conflicting recommendations made by various medical entities (ACS 2010; Burford 2010; AUA 2009; RACGP 2012; USPSTF 2012). Screening for prostate cancer may reduce both morbidity and mortality, yet the best method of screening (if any) is unknown. Equally, screening

may promote treatment procedures that are unwarranted or may adversely affect the health outcomes of the patient, resulting in no net benefit or even net harm. The cost-benefits associated with screening and potential follow-up tests and treatment may be justified; however, the economic implication of prostate cancer screening remains unknown. Additionally, only a single trial of treatment versus observation for early stage, screen-detected prostate cancer has been reported (Wilt 2012).

Evidence on the effectiveness of treatment for prostate cancer is conflicting. An evaluation of radical prostatectomy versus watchful waiting in early prostate cancer in the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) identified that, after 15 years, radical prostatectomy reduced disease-specific mortality, overall mortality, and risk of metastasis (Bill-Axelson 2011). Reductions in overall and disease-specific mortality and metastatic disease were limited to men less than 65 years of age. Conversely, a similar trial evaluating radical prostatectomy versus observation in localised prostate cancer reported that radical prostatectomy did not significantly reduce all-cause or prostate cancer-specific mortality when compared to observation (Wilt 2012). Sakr and colleagues have estimated that close to half of men aged over 50 years have histological evidence of prostate cancer, with this figure rising to close to 80% of men aged up to 80 years (Sakr 1996). Despite this high prevalence, prostate cancer is not commonly diagnosed as the primary cause of mortality in these men (Parkin 2005; Sakr 1996).

In addition, there have been a number of population-based studies to examine the potential impact of prostate cancer screening that are frequently cited in favour of prostate cancer screening (Bartsch 2001; Jacobsen 1998; Kopec 2005; van Leeuwen 2010). Findings of these studies are not temporally or geographically consistent with a screening effect; for example, the decline in prostate cancer mortality seen in the United States that began shortly after the initiation of widespread PSA screening is likely to predate any plausible impact due to PSA testing given the long time to any potential benefit (that is 10 years). These studies are at high risk for confounding, most notably selection bias and lead and length-time bias, which can only be adequately controlled for in a randomised controlled trial. These factors emphasize the importance of a systematic review of randomised trials for guiding individual patient, provider, and health policy decision-making.

The first version of this Cochrane review (published in 2006) concluded that there was insufficient evidence to either support or refute the use of routine mass, selective, or opportunistic screening for prostate cancer. An update of the review in 2010 identified three additional trials, which were included in the review. Meta-analysis of the five studies included in the 2010 review concluded that screening did not significantly reduce prostate cancer-specific mortality. Since the last update, several studies have provided follow-up data. This 2012 version of the review incorporates the latest updates to the literature to examine the current evidence and evaluate the absolute benefits and harms associated with screening for prostate cancer. We have rated the quality of the evidence by outcome according to GRADE and include a summary of findings table.

OBJECTIVES

The primary objective of this review was to determine the efficacy of screening men for prostate cancer in reducing prostate cancer-specific and all-cause mortality.

The secondary objectives of this review were to:

- determine the impact of prostate cancer screening on quality of life and adverse effects; and
- document the costs of screening for prostate cancer.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised, and quasi-randomised, controlled trials of screening versus no screening for prostate cancer were eligible for this review. No language restrictions were placed on studies considered for inclusion in this review, and published or unpublished sources were considered.

Types of participants

All men enrolled in studies of prostate cancer screening were eligible for this review, with no exclusions based on ethnicity, age, or presence of lower urinary tract symptoms. Studies including men with a previous diagnosis and treatment of prostate cancer were excluded.

Types of interventions

Studies that used any of the following screening procedures, individually or in combination, were included:

- digital rectal examination (DRE);
- prostate-specific antigen (PSA) test (including total, velocity, density, and percentage free and complex); and
- transrectal ultrasound (TRUS)-guided biopsy.

Types of outcome measures

The following outcomes were measured.

Primary outcomes

Primary outcome measures for this review were prostate cancer-specific and all-cause mortality.

Secondary outcomes

Secondary outcome measures included:

- incident prostate cancers by stage and grade at diagnosis;
- metastatic disease at follow-up;
- quality of life;
- harms of screening (including both adverse outcomes from false-positive or false-negative results and their impact upon resulting treatment procedures); and
- costs associated with screening programs.

Search methods for identification of studies

A combination of electronic and manual searches were conducted for this review.

Electronic searches

Electronic searches of the PROSTATE register (made available by the Cochrane Prostatic Diseases and Urologic Cancers Group), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CANCERLIT, and the NHS EED. For the original version of this review the PROSTATE register was initially searched in November 2004, with the remaining databases searched for studies published between 1966 and January 2006. There was no restriction on language in any searches. The search strategy is provided in 'Appendix 1' and was adapted for each electronic database.

An updated search of the electronic databases was previously performed with the existing search strategy in July 2010. A further search of the electronic databases was performed for this current version of the review in June 2012.

Searching other resources

Handsearching for reviews and technical reports with regard to prostate cancer screening in specialist journals, as shown below, and grey literature was conducted in the original version of the review.

The following journals were handsearched until March 2005:

- *BJU International* (2000 to 2005);
- *European Urology* (2002 to 2005);
- *The Prostate* (1998 to 2005);
- *The Journal of Urology* (1996 to 2005);
- *Urology* (2002 to 2005);
- *Cancer* (1998 to 2005).

Authors of studies that were included in this review were contacted in order to request additional study information, as needed.

The authors of a 2010 BMJ (Djulbegovic 2010) systematic review of screening for prostate cancer performed a manual search of abstracts presented at the following meetings (from 2005 to 2010):

- American Urological Association (AUA);
- European Association of Urology (EAU);
- American Society of Clinical Oncology (ASCO).

This present review contains authors from both the original Cochrane review and the BMJ review. As such, it was decided that handsearching of the grey literature would continue based on the proceedings from the AUA, EAU, and ASCO meetings. For the purposes of this update, handsearching was performed for abstracts presented at the AUA, EAU, and ASCO meetings from 2010 to 2012.

Data collection and analysis

The authors followed the recommended strategies for data collection and analysis as documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two of the authors (DI and PD) independently selected trials for possible inclusion against a pre-determined checklist of inclusion criteria. Studies were initially categorized into the following groups:

- possibly relevant, studies that met the inclusion criteria and studies for which it was not possible to determine whether they met the criteria either from their title or abstract;
- excluded, those clearly not meeting the inclusion criteria.

If a title or abstract appeared to meet the eligibility criteria for inclusion in the review, or we could not determine eligibility, a full-text version of the article was obtained and assessed by two authors (DI and PD) in order to determine whether it met the inclusion criteria. Discrepancies between the authors were resolved via discussion.

Data extraction and management

Two authors (DI and MMN) independently extracted data using a standard data extraction form. Any discrepancies between the review authors were resolved by consensus. The data extraction form was pilot tested and modified accordingly before use. In addition to the quality characteristics and the results of the trial, the following details were recorded:

- participant details, including demographic information and inclusion and exclusion criteria;
- types of screening interventions used and their comparison;
- outcomes reported, including the types of measure used to record the outcome.

Assessment of risk of bias in included studies

In the original review, the risk of bias was assessed by reporting the trial's conduct against the following key criteria:

- randomisation;
- allocation concealment, as coded according to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005);
- blinding of participants (graded as yes, no, or unclear);
- blinding of outcome assessors (graded as yes, no, or unclear);
- completeness of the follow-up, i.e. description of any numbers of participants lost to follow-up (graded as yes, no, or unclear); and
- whether or not an intention-to-screen analysis was performed (graded as yes, no, or unclear).

Trials were categorized as attributing a 'low', 'moderate', or 'high' risk of bias (Higgins 2005).

In this updated review, assessment of risk of bias was made using the Cochrane Collaboration's tool for assessing risk of bias, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two authors (DI and MMN) independently assessed the susceptibility to bias of the selected trials. Risk of bias in this review was assessed by reporting the trial's conduct against the following key criteria:

- sequence generation;
- allocation concealment;
- blinding of participants, personnel, and outcome assessors;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias (defined as inappropriate data analysis).

Each criterion was assessed by a question-based entry, with the judgement being 'yes' indicating 'low' risk of bias, 'no' indicating a 'high' risk of bias, and 'unclear' (Higgins 2011). Overall risk of bias was summarised with consideration to the relative importance of domains and empirical evidence of bias. Risk of bias for each study was summarised as: (i) 'low' risk of bias, when a low risk of bias was described for all key domains; (ii) 'unclear' risk of bias, when the bias was deemed to be unclear in one or more of the domains; and (iii) 'high' risk of bias, when one or more domains were judged to be of a high risk of bias (Higgins 2011). Included studies were abstracted independently by the two authors using an abstraction form detailing the above mentioned criteria. Any discrepancies were discussed between the authors.

Additionally, the GRADE framework was applied to rate the quality of evidence for each outcome, with results reported in a summary of findings table (Guyatt 2011; Schünemann 2011). Evidence rated as 'high' quality means that further research is very unlikely to change our confidence in the estimate of effect, while a 'moderate' quality rating means further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Similarly, an evidence rating of 'low' quality means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. A 'very low' quality evidence rating means that we are very uncertain about the estimate.

Measures of treatment effect

Statistical analysis was performed according to the statistical guidelines referenced in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For dichotomous outcomes, the measure of effect is expressed as a risk ratio (RR) and absolute risk (AR) with 95% confidence intervals (CI); and for continuous outcomes, the measure of effect is expressed as a weighted mean difference with 95% CI. In the event that continuous data were reported on different continuous scales, outcomes were standardised, where possible, to calculate the standardised mean difference. Where data were available, and if the trial did not report intention-to-screen analysis results, we performed intention-to-screen analyses using the groups to which the participants were originally randomised (that is screening versus control).

Dealing with missing data

Any missing data were dealt with by contacting the original study investigators to request the missing data. In the event that missing data were not available to the review authors, analysis was performed on the available data.

Assessment of heterogeneity

Heterogeneity was analysed by graphical interpretation of the forest plot and with the I^2 statistic. An I^2 value above 75% was considered to be an indicator of considerable heterogeneity (Higgins 2011). We also evaluated studies for clinical heterogeneity, focusing primarily on patient characteristics (for example age) and screening and subsequent treatment protocols (for example PSA screening intervals and thresholds for additional evaluation).

Assessment of reporting biases

Funnel plots were used in exploratory data analyses to assess for possible reporting and small study biases. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design of small studies, and publication bias (Sterne 2001).

Data synthesis

We used the random-effects model to determine the effect of screening on prostate cancer mortality using the Cochrane Collaboration's RevMan 5.1 software (RevMan 2011).

Subgroup analysis and investigation of heterogeneity

Due to the nature of the studies, we were not able to do a subgroup analysis based on screening intervention (DRE versus TRUS versus PSA). Since the prevalence of prostate cancer increases with age and the potential effectiveness of screening may also vary according to age, a subgroup analysis exploring screening of men aged greater than or equal to 45, 50, and 55 years of age was performed for this updated review.

Sensitivity analysis

Sensitivity analyses were performed to investigate the impact of risk of bias (for sequence generation and allocation concealment) of included studies on robustness of results. Sensitivity analyses were also performed to assess overall risk of bias by outcome. A post hoc sensitivity analysis excluding the Stockholm study was performed as the external validity of the Stockholm study was assessed as low since patients were only screened once. Additionally, the screening process and thresholds used in the study are not currently employed in clinical practice. A post hoc sensitivity analysis was also performed including the French centre in the European Randomised Study of Screening for Prostate Cancer (ERSPC) data for the outcomes of prostate cancer diagnosis, localised tumour stage, and advanced tumour stage, as mortality data from the French centre were not available. The ERSPC study did not include data from the French study centre either in mortality analyses, due to short duration of follow-up, or in primary analyses of other outcomes.

RESULTS

Description of studies

Five randomised controlled trials (RCTs) (ERSPC; Norrkoping; PLCO; Quebec; Stockholm) comparing mass screening for prostate cancer to no screening were identified as meeting the inclusion criteria for this review. All studies reported on prostate cancer-specific mortality as the primary outcome. Additional reported outcomes included prostate cancer diagnosis, all-cause mortality, clinical stage, Gleason score, and treatment follow-up. The ERSPC and Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial studies provided some data on number of biopsies performed and harms associated with screening (for example infection and bleeding from TRUS-guided biopsies). For further descriptive information about the studies, refer to the 'Characteristics of included studies' table.

Results of the search

The search in the original review returned 1965 citations identified by the search of MEDLINE (1966 to October 2006), of which 98 were selected for full-text review. Searches of EMBASE, CANCERLIT, PROSTATE, NHS EED, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, Issue 1), and

bibliographies of reviewed articles did not reveal any further relevant studies that were not previously identified through the MEDLINE search. Handsearching of identified journals revealed one relevant study not identified through the electronic searches (Norrkoping). Of the 99 studies selected for further review, 52 were cohort studies, 19 were narrative reviews or commentaries, and five were studies reporting data from pilot studies, or associated data, from the ongoing multi-centre ERSPC trial. Two studies ultimately met the selection criteria and were included in the original 2006 review (Norrkoping; Quebec).

The updated search in July 2010 yielded 366 citations, of which 106 were selected for full-text review. Three new studies met the selection criteria and were included in the 2010 updated review (ERSPC; PLCO; Stockholm). The remaining studies consisted of 17 RCTs on topics incorporating elements of prostate cancer but not investigating the effect of screening on mortality; 31 cohort and case-control or other comparative studies; 25 reviews, guidelines, or protocols; one editorial; and 29 studies associated with either the ERSPC or PLCO studies included in this review. An additional longer-term follow-up, site-specific report on the Swedish arm of the ERSPC study was also included in the 2010 updated review, and the results incorporated with the other sites that formed the ERSPC study.

The updated search in June 2012 yielded 855 citations, of which 31 were selected for full-text review. Twenty studies were excluded, with 10 of these reporting an outcome not relevant to the aims of this systematic review, and 10 reporting findings that were incorporated in other publications of the ERSPC. Three studies reporting updates of the ERSPC, PLCO, and Norrkoping studies were included, along with two studies referring to the ongoing Comparison Arm for ProtecT (CAP) study. A further four studies were included as part of the ERSPC study, with two further studies included as part of the PLCO study.

Included studies

Five RCTs were included in the review, with significant differences in the methodological design between them. The Norrkoping study recruited men 50 to 69 years of age in Sweden and screened every three years. During the initial phase of the study, only the DRE was offered, however the screening regimen later evolved to include DRE and PSA. A PSA level greater than 4.0 ng/mL was deemed the cut-off for biopsy. Participants were followed up over a 20-year period. The Quebec study recruited men 45 to 80 years of age in Canada and provided annual screening with combination DRE and PSA. A PSA greater than 3.0 ng/mL was deemed the cut-off for biopsy. Participants were followed up over an 11-year period. The Stockholm study recruited men aged 55 to 70 years in Sweden for a one-time screening using DRE, PSA, and TRUS. A PSA greater than 10.0 ng/mL was deemed the cut-off for biopsy, with repeat TRUS performed for PSA greater than 7.0 ng/mL. Participants were followed up over a 15-year period. The PLCO study recruited men aged 55 to 74 years in the United States for annual screening with DRE and PSA. A PSA greater than 4.0 ng/mL was deemed possibly indicative of prostate cancer and patients were advised to seek diagnostic evaluation. Participants were followed up over a 10- to 13-year period. The ERSPC recruited men ranging in age from 50 to 74 years across nine European countries. Screening regimens varied across participating sites, with cut-off values for biopsy ranging from a PSA greater than 2.5, to 3.0, 4.0, and 10.0 ng/mL. Screening interval in six of the sites was every four years. For further information on included studies, see the 'Characteristics of included studies' table for further details.

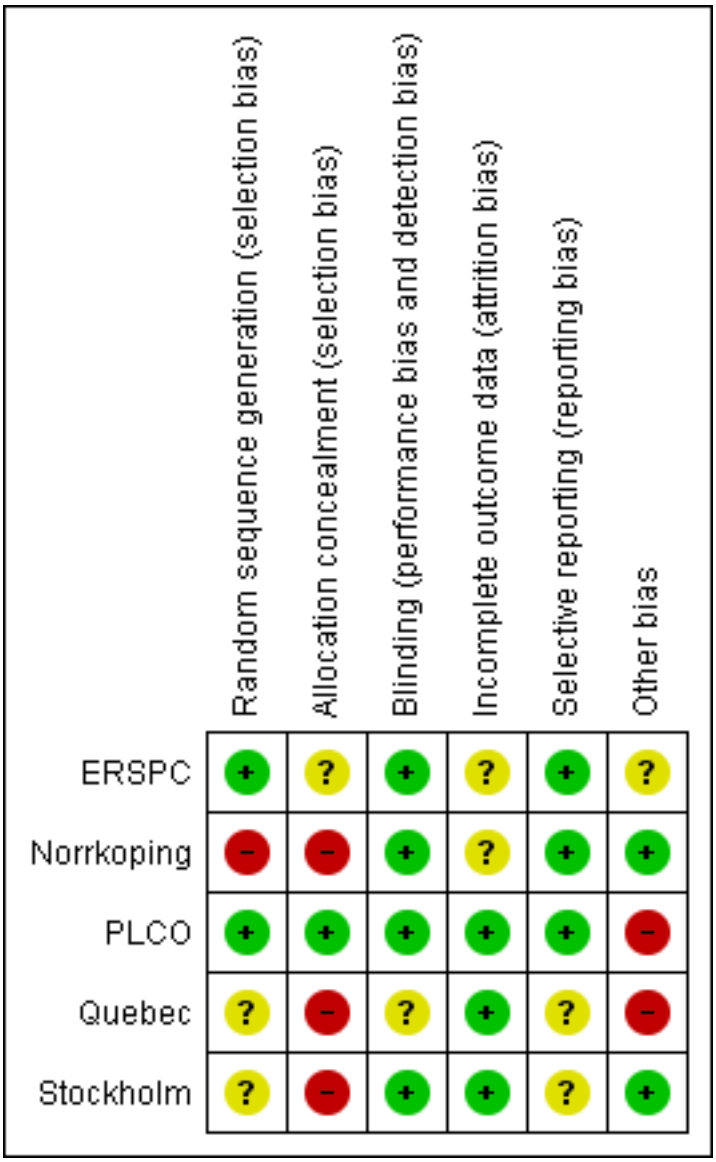
Excluded studies

Studies were primarily excluded because they were not RCTs, or because they did not provide data specific to the primary and secondary outcomes of this systematic review. See the 'Characteristics of excluded studies' section for further information.

Risk of bias in included studies

Assessment for risk of bias of each included study is described in the 'Characteristics of included studies' section. Risk of bias is also represented graphically in 'Figure 1'. The risk of bias as determined for each included study was as follows.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



- ERSPC: low risk of bias (majority of domains were low risk of bias, with the exception of the allocation concealment domain (unclear risk of bias), incomplete outcome data domain (unclear risk of bias), and other bias domain (unclear risk of bias)). Although an early pilot study indicated that adequate allocation concealment was used during the study, limited data were given on the details of allocation concealment across participating study sites (Schröder 1996).
- Norrkoping: high risk of bias (due to high risk associated with the allocation sequence generation and allocation concealment, as well as uncertainty about incomplete outcome data).
- PLCO: low risk of bias (majority of domains were low risk of bias, with the exception of the other bias domain due to high control group contamination (high risk of bias)).
- Quebec: high risk of bias (due to high risk of bias associated with allocation concealment and analysing data not using the intention-to-treat principle, as well as uncertainty about random sequence generation, blinding of outcome assessors, and selective reporting).
- Stockholm: high risk of bias (due to high risk associated with allocation concealment, and uncertainty with sequence generation and selective reporting). This study also had low external validity as it had a one-time screen for prostate cancer, with biopsy only performed if the PSA value was greater than 10 ng/mL.

Authors were contacted via e-mail to assist with the assessment for risk of bias of the included studies, as needed. Sensitivity analysis was performed on all outcomes to account for overall study risk of bias.

The quality of the evidence was rated as 'moderate' according to GRADE for all-cause mortality, prostate cancer-specific mortality, and advanced tumour stage; and 'low' for prostate cancer diagnosis and localised tumour stage (Guyatt 2011; Schünemann 2011) ('Summary of findings for the main comparison').

Allocation

Sequence generation was clearly described in the ERSPC and PLCO studies. The ERSPC trial used random number generators, while the PLCO study used a computerised randomisation scheme. The method of concealment was unclear for the ERSPC study. It also was not clear whether the method of concealment was uniform across all participating sites. The PLCO study achieved concealment through use of a central system. The method of sequence generation was unclear for the Quebec and Stockholm studies as the authors did not mention what process of sequence generation was used. The Norrkoping study did not have adequate sequence generation, as men were randomised according to a list of dates of births.

As the ERSPC and PLCO studies were assessed as at overall low risk of bias, no other additional sensitivity analysis (beyond that for overall risk of bias) was performed specifically for individual criteria such as risk of bias in the generation of the random sequence (where both studies were the only studies to be rated as low risk of bias) or allocation concealment (where only the PLCO study was assessed as being low risk of bias).

Blinding

Participants and clinicians were not blinded to the screening intervention. Methods to blind outcome assessment were adequately described for all but one study (Quebec).

Incomplete outcome data

The Quebec, Stockholm, and PLCO studies provided complete data, with any withdrawal cited and explained. Withdrawals were cited for the Norrkoping study, however it was unclear how data for men who participated but migrated out of the catchment area were obtained. The ERSPC study consisted of nine study centres, but it did not include data from the French study centre either in mortality analyses, due to short duration of follow-up, or in primary analyses of other outcomes; and the Portuguese centre was excluded due to discontinuation. The ERSPC data in this review were therefore based on seven ERSPC centres.

Selective reporting

The ERSPC, Norrkoping, and PLCO studies were determined to be at low risk of bias for selective reporting as determined by comparisons between previously published protocols for the respective studies and the current published data. It was not possible to assess selective reporting for the remaining two studies due to insufficient information.

Other potential sources of bias

A preliminary article on the ERSPC study reported that a consensus workshop was formed to structure specific components of the study. It was decided that an age range of 55 to 70 years was determined as being the 'core' age group for participants, with the inclusion of higher or lower age groups, or both, being left to the discretion of the participating centres (Schröder 2003). Another preliminary paper also stated that the primary endpoint of the ERSPC study will be the prostate cancer mortality rate in the total study arm compared with the control arm; with one analysis to be conducted for the 'core' age group (men aged 55 to 69 years at entry to the trial) and another for all ages at entry (de Koning 2003). It was also described that the ERSPC study had sufficient power to detect a significant difference in prostate cancer mortality between the total study arm compared with the control arm if the true reduction in mortality by screening was 25% or more, or if contamination was limited to 10% if the true effect is 20% or more (de Koning 2002b; Schröder 2003). It has since been estimated that the contamination rate in the ERSPC study was 30.7%, accounting for 27,431 out of 89,353 men in the control group having at least one PSA test (Roobol 2009). Similarly, the PLCO study reported that 45% of participants entered the study with a history of PSA screening in the three years prior to randomisation, with subsequently 52% of men assigned to the control group undertaking some form of screening during the study period.

There were also changes to the screening protocol of the ERSPC study, where both the DRE and TRUS ceased to be used as screening tests in 1997 (Schröder 2003). The PSA cut-off value was also reduced to 3.0 ng/mL during this time, however several centres continued to use a PSA value of 4.0 ng/mL as the cut-off, or applied ancillary tests if PSA test values were within a certain range (for example men in the Italian centre with a PSA value of 2.5 to 3.9 ng/mL underwent DRE and TRUS) (ERSPC; Schröder 2003).

Data were not analysed according to the intention-to-screen principle in the Quebec study. From a total of 31,133 men randomised to the screening group, only 7348 (23.6%) were actually screened (that is all 31,133 men were invited to be screened but only 23.6% took up the invitation and actually were screened). Similarly, of the 15,353 men randomised to the control group, 1122 (7.3%) were screened for prostate cancer at the study site. The data were extracted and re-analysed for this review according to the intention-to-screen principle by the authors of this review.

Funnel plots for all outcomes were symmetrical; however, the results using this tool were still interpreted with caution.

Effects of interventions

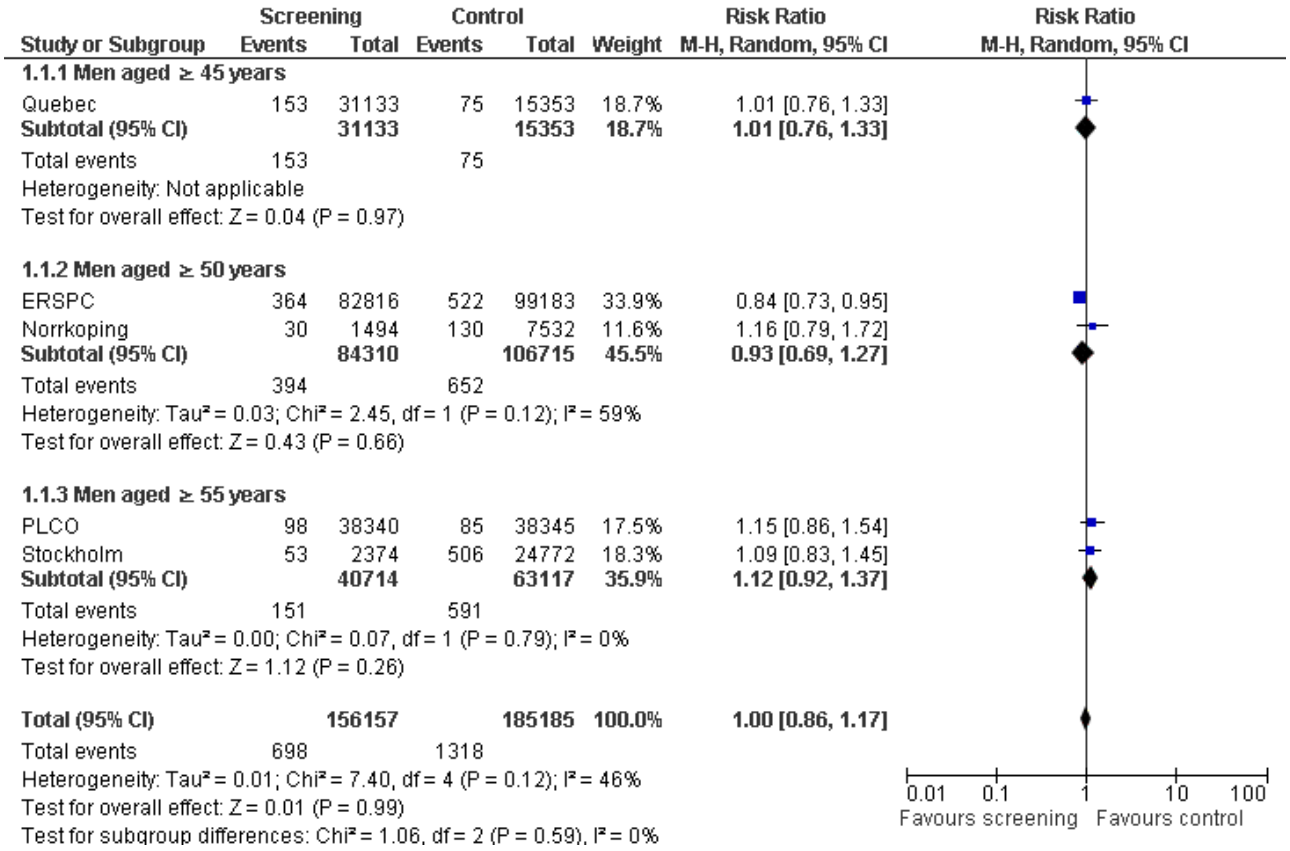
See: **Summary of findings for the main comparison** Screening for prostate cancer

Prostate cancer-specific mortality

Results of meta-analysis

Prostate cancer screening did not result in a statistically significant reduction in prostate cancer-specific mortality when all populations of all studies were analysed according to intention-to-screen analysis. Meta-analysis of the five included trials identified the risk ratio of prostate cancer-specific mortality to be 1.00 (95% CI 0.86 to 1.17) ('Figure 2'). Our analysis of the five studies showed no statistically significant reduction in prostate cancer-specific or all-cause mortality among the whole population of men randomised to screening versus controls. The ERSPC demonstrated a marginally significant benefit for screening in reducing prostate cancer-specific mortality among a 'core' subgroup of men aged 55 to 69 years at baseline (RR 0.79, 95% CI 0.69 to 0.92) over a median follow-up duration of 11 years ('Analysis 1.2'). The other 'low' risk of bias study, PLCO, demonstrated no significant benefit for screening through 10 years of follow-up (RR 1.15, 95% CI 0.86 to 1.54). A meta-analysis incorporating the 'core age group' in the ERSPC study identified the RR of prostate cancer-specific mortality to be 1.00 (95% CI 0.83 to 1.19) ('Analysis 1.2'). Sensitivity analysis demonstrated no significant difference on results with the inclusion or exclusion of the Stockholm study.

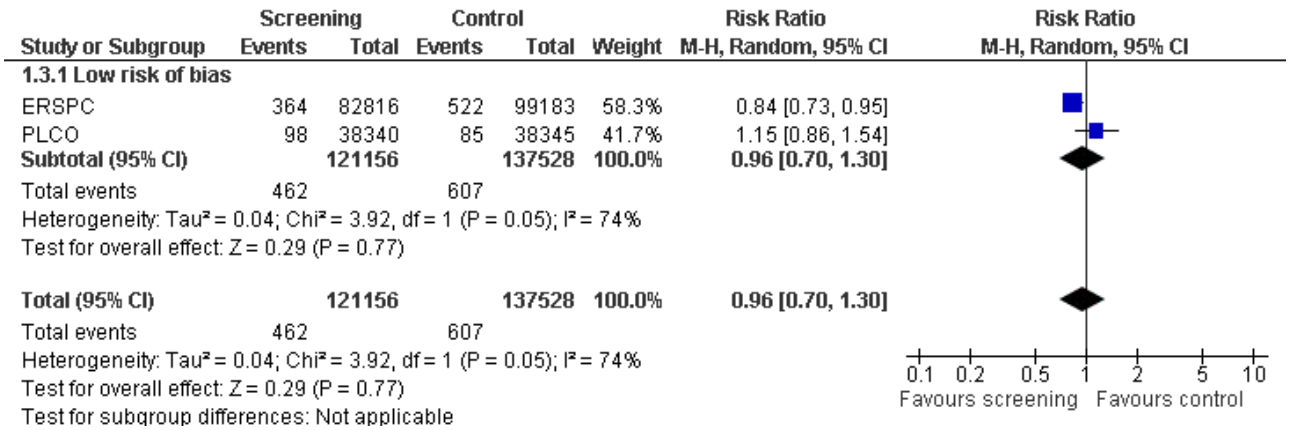
Figure 2. Forest plot of comparison: 1 Screening versus control, outcome: 1.3 Prostate cancer-specific mortality (subgroup analysis age)



Risk of bias sensitivity analysis

The quality of evidence was rated as moderate for this outcome ('Summary of findings for the main comparison'). Both the ERSPC and the PLCO studies were assessed as at low risk of bias, whilst the Norrkoping, Quebec, and Stockholm studies were assessed as high risk of bias. Meta-analysis of the two low risk of bias studies produced a RR of 0.96 (95% CI 0.70 to 1.30) ('Figure 3'). Using data from the 'core age group' of the ERSPC study produced a RR of 0.94 (95% CI 0.65 to 1.35) ('Analysis 1.4').

Figure 3. Forest plot of comparison: 1 Screening versus control, outcome: 1.3 Prostate cancer-specific mortality (sensitivity analysis overall risk of bias).



Subgroup analysis

Subgroup analysis explored prostate cancer-specific mortality according to age. It identified no significant difference in prostate cancer-specific mortality when men were screened from 45 years of age (RR 1.01, 95% CI 0.76 to 1.33), 50 years of age (RR 0.93, 95% CI 0.69 to 1.27), or 55 years of age (RR 1.12, 95% CI 0.92 to 1.37) ('Figure 2'). A second meta-analysis was performed, which incorporated the 'core age group' of men from the ERSPC study (that is men aged 55 to 69 years). Conducting a meta-analysis using this approach demonstrated no significant difference in prostate cancer-specific mortality across any of the age groups ('Analysis 1.2').

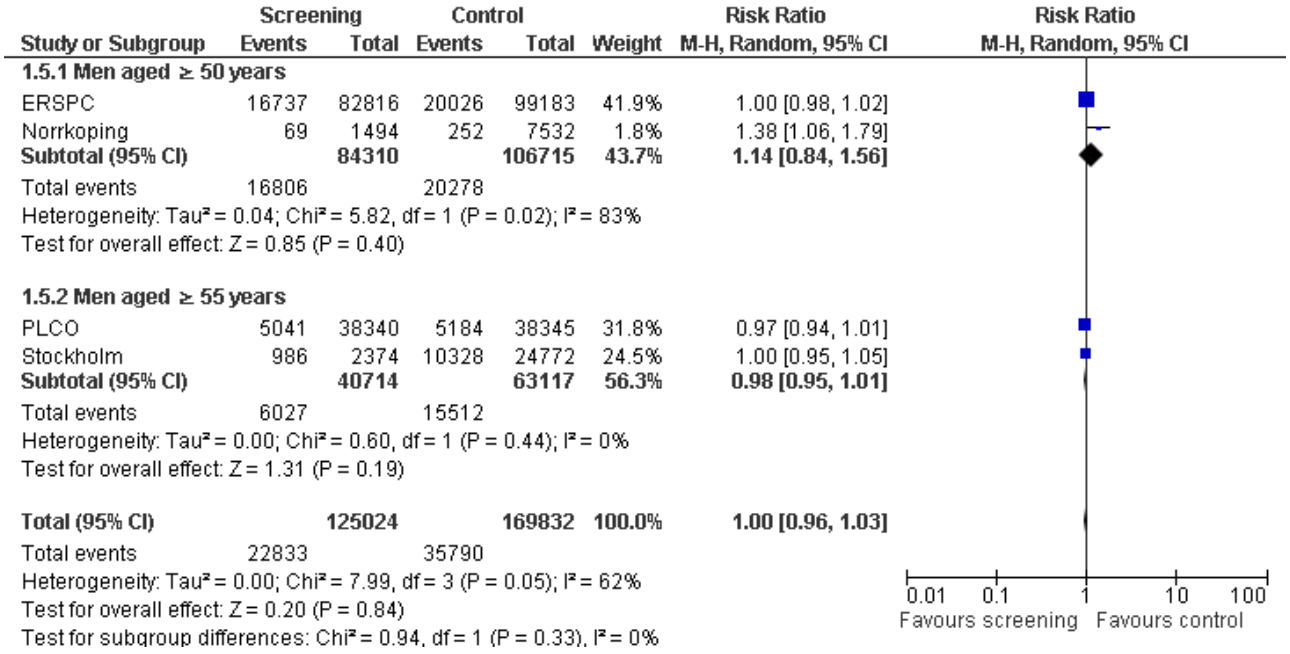
Participant characteristics including race or ethnicity; family history of prostate cancer; enlarged prostate (or BPH); previous prostate biopsy, PSA, or DRE were only reported in the PLCO study.

All-cause mortality

Results of meta-analysis

Prostate cancer screening did not result in a statistically significant reduction in all-cause mortality. A meta-analysis of four studies (ERSPC; Norrkoping; PLCO; Stockholm) demonstrated no difference in all-cause mortality between the screening and control groups (RR 1.00, 95% CI 0.96 to 1.03) ('Figure 4'). This result did not differ when the data from the 'core age group' of the ERSPC study were used (RR 0.99, 95% CI 0.96 to 1.03) ('Analysis 1.6'). Sensitivity analysis demonstrated no significant difference in results with the inclusion or exclusion of the Stockholm study.

Figure 4. Forest plot of comparison: 1 Screening versus control, outcome: 1.5 All-cause mortality (subgroup analysis age).



Risk of bias sensitivity analysis

The quality of evidence was rated as moderate for this outcome ('Summary of findings for the main comparison'). The ERSPC and PLCO studies were assessed as at low risk of bias. Conversely, the Stockholm and Norrkoping studies were graded as at high risk of bias. Sensitivity analysis demonstrated no significant difference in results with the inclusion or exclusion of the Stockholm and Norrkoping studies ('Analysis 1.7'; 'Analysis 1.8').

Subgroup analysis

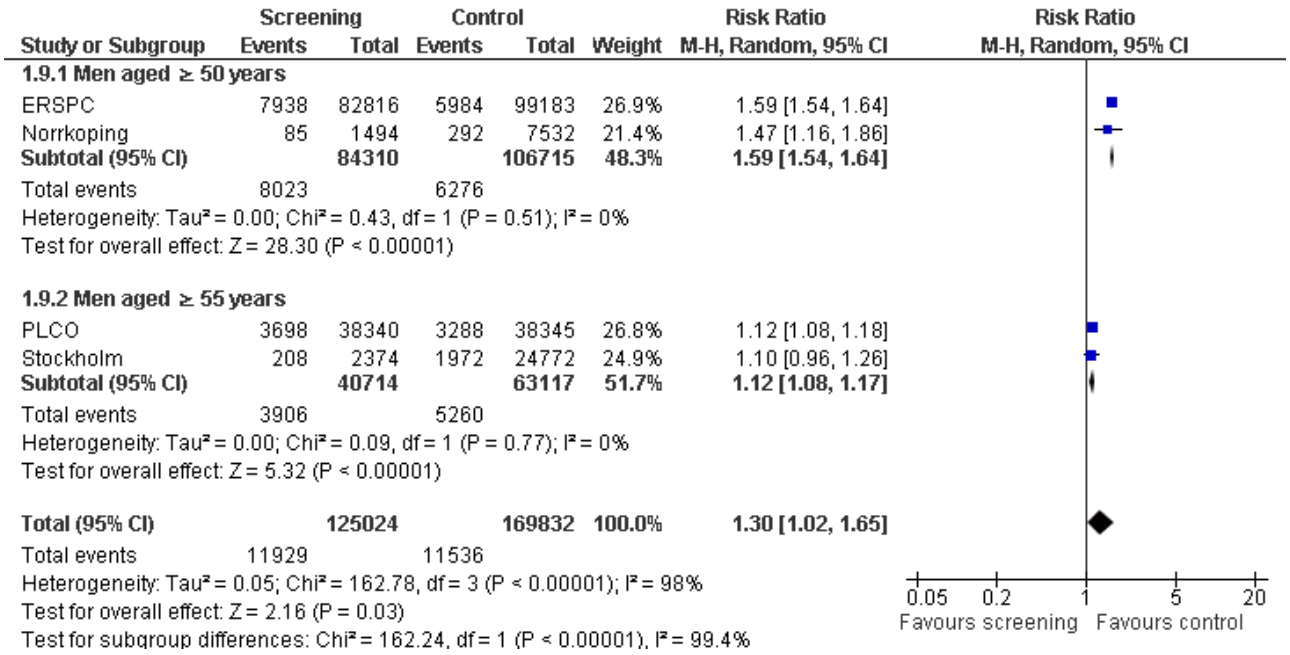
Subgroup analysis explored all-cause mortality according to age ('Figure 4'). It identified no significant difference in all-cause mortality in men aged 50 years and above (RR 1.14, 95% CI 0.84 to 1.56) or men aged 55 years and above (RR 0.98, 95% CI 0.95 to 1.01). A second meta-analysis incorporating the 'core age group' from the ERSPC study demonstrated a significant difference in all-cause mortality only in men aged 50 years and above (RR 1.38, 95% CI 1.06 to 1.79), and this was based on the Norrkoping study alone ('Analysis 1.6').

Diagnosis of prostate cancer (as determined by study)

Results of meta-analysis

Prostate cancer screening increased the number of men diagnosed with prostate cancer. The number of men diagnosed with prostate cancer across both the screening and control groups was reported by four of the included studies. Meta-analysis of the ERSPC, Norrkoping, PLCO and Stockholm trials indicated that screening was associated with a 30% increase in the number of men diagnosed with prostate cancer (RR 1.30, 95% CI 1.02 to 1.65) ('Figure 5'; 'Analysis 1.10'). Incorporating data from the French site of the ERSPC study resulted in no change in those findings (RR 1.26, 95% CI 1.06 to 1.51).

Figure 5. Forest plot of comparison: 1 Screening versus control, outcome: 1.9 Prostate cancer diagnosis (subgroup analysis age).



In the ERSPC study, a total of 16.6% of screening tests were assessed as positive in the 'core age group', with 85.9% of men with positive tests undergoing a biopsy. In the PLCO study, a total of 7.5% of men tested positive for a DRE and 7.9% for a PSA test, with 74% undertaking further diagnostic evaluation and 31.5% of men undergoing a biopsy within one year of screening.

Statistical heterogeneity was high for this outcome. Sensitivity analysis (using a fixed-effect model for the meta-analysis) demonstrated no significant difference in results (RR 1.40, 95% CI 1.37 to 1.44). Clinical heterogeneity was apparent with the Stockholm study, as the screening procedures adopted in that study differed considerably from the other included studies. Sensitivity analysis demonstrated no significant difference in results with the inclusion or exclusion of the Stockholm study.

Significant heterogeneity was associated with the meta-analyses for prostate cancer diagnosis. Performing a meta-analysis only according to age group significantly reduced the heterogeneity (see below).

Risk of bias sensitivity analysis

The quality of evidence was rated as low for this outcome ('Summary of findings for the main comparison'). Both the ERSPC and PLCO studies were assessed as at low risk of bias. The Norrkoping and Stockholm studies were graded as at high risk of bias. Sensitivity analysis demonstrated no meaningful difference in results with the exclusion of the Norrkoping and Stockholm studies.

Subgroup analysis

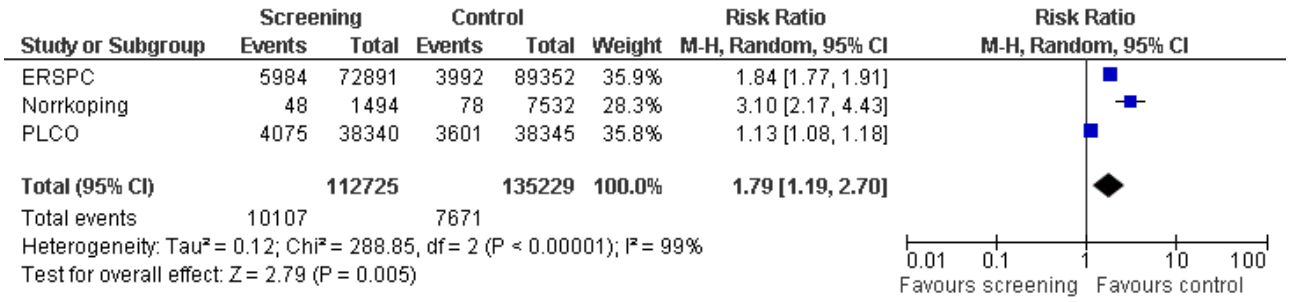
A subgroup analysis was performed with respect to the age at which men were first screened for prostate cancer. A meta-analysis of the ERSPC and Norrkoping studies, for men screened aged 50 years or older, provided a RR of 1.59 (95% CI 1.54 to 1.64), with an I^2 of 0% ('Figure 5'). A meta-analysis of the PLCO and Stockholm studies, for men screened aged 55 years or older, provided a RR of 1.12 (95% CI 1.08 to 1.17), with an I^2 of 0% ('Figure 5').

Prostate tumour stage

Results of meta-analysis

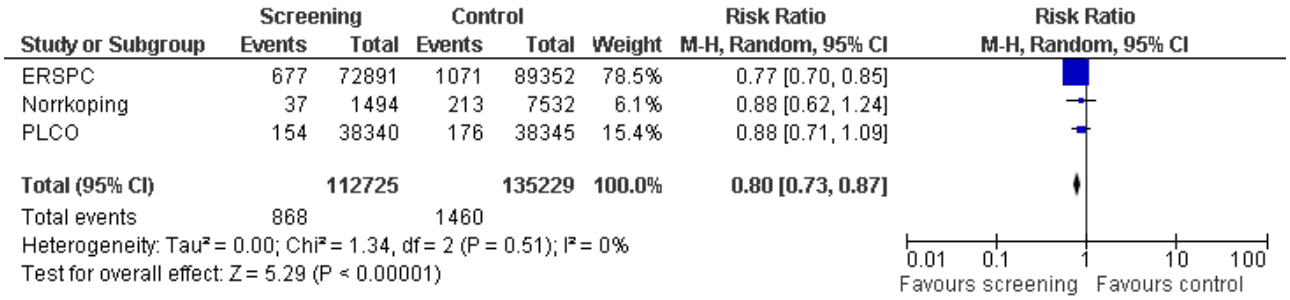
A meta-analysis of the ERSPC, Norrkoping, and PLCO studies indicated that the proportion of men diagnosed with localised prostate cancer was significantly greater in the screening group compared to the control group (RR 1.79, 95% CI 1.19 to 2.70) ('Figure 6'). Incorporating data from the French site of the ERSPC study resulted in no change in these findings (RR 1.66, 95% CI 1.22 to 2.27).

Figure 6. Forest plot of comparison: 1 Screening versus control, outcome: 1.11 Tumour stage (localised T1-T2, N0, M0).



Conversely, the proportion of men diagnosed with advanced prostate cancer was significantly lower in the screening group compared to men in the control group (RR 0.80, 95% CI 0.73 to 0.87) ('Figure 7'). Incorporating data from the French site of the ERSPC study resulted in no change in these findings (RR 0.77, 95% CI 0.71 to 0.83). The eight-year follow-up publication of the Quebec study reported stage distribution in the screened cohort at the first and follow-up visit ('Table 1').

Figure 7. Forest plot of comparison: 1 Screening versus control, outcome: 1.12 Tumour stage (advanced T3-4, N1, M1).



Risk of bias sensitivity analysis

The quality of evidence was rated as low for localised prostate cancer and moderate for advanced prostate cancer ('Summary of findings for the main comparison'). Both the ERSPC and PLCO studies were assessed as at low risk of bias, whereas the Norrkoping study was graded as at high risk of bias. Sensitivity analysis, with the exclusion of the Norrkoping study, demonstrated a reduction in the effectiveness of screening in detecting localised prostate cancer (RR 1.44, 95% CI 0.90 to 2.32) but no effect on advanced cancer.

Harms of screening

Prostate cancer screening resulted in a range of harms that can be considered minor to major in severity and duration. Common minor harms from screening include bleeding, bruising, and short-term anxiety. Common major harms include overdiagnosis and overtreatment, including infection, blood loss requiring transfusion, pneumonia, erectile dysfunction, and incontinence.

In total, 26,492 positive PSA tests were recorded in the ERSPC study, with a further 22,699 biopsies performed. No deaths were reported as a direct complication (from issues such as septicaemia or bleeding) from the biopsy procedure. Causes of death in the 14 men who were biopsied and subsequently died within 120 days included intercurrent death not as a result of biopsy (2), ischaemic heart disease (6), lung cancer (1), pancreatitis and myocarditis (1), subdural haematoma (1), basilar artery thrombosis (1), unknown (1), and a combination of issues (1) (ERSPC). The most common complications assessed as 'minor' were haematospermia and haematuria for greater than three days, whilst the most common side effects assessed as 'major' complications were pain after biopsy and fever (Raaijmakers 2002). Based on these biopsies, 7938 (9.6%) of 82,816 men in the screening group were diagnosed with prostate cancer; with 2483 (31.3%) of 7938 biopsied men diagnosed with prostate cancer outside of the screening protocol. The false-positive rate for men who had an elevated PSA value (different PSA thresholds were used to define elevated but typically the threshold was defined as > 3.0 ng/mL) was 17.8% for men screened at least once in the ERSPC study, compared to a detection rate of 3.4% to 3.6% (ERSPC). The rate of overdiagnosis in the screening group was estimated to be up to 50% (ERSPC).

The PLCO study similarly reported on adverse events for screening and treatment, with a false-positive rate of 10.4% and 15.0% for screening with the PSA test and DRE, respectively (PLCO). Pain or bleeding was associated with a rate of 0.3 per 10,000 screenings with DRE. The PSA test had a complication rate of 26.2 per 10,000 screenings (primarily dizziness, bruising, and haematoma; with three episodes of fainting). Medical complications from the diagnostic procedures occurred in 68 of 10,000 evaluations after a positive result from screening. These complications were primarily infection, bleeding, clot formation, and urinary difficulties.

The ongoing CAP study also reported a variety of harms associated with screening (Rosario 2012). Immediate short-term adverse events (< 30 days) include mild or no pain (85%), dizziness (3%), and haematuria (7%). Moderate adverse events (up to 35 days post-biopsy) include pain (44%), fever (20%), haematuria (66%), haematochezia (37%), and haemoejaculate (90%). Long-term adverse events (≥ 2 weeks post-biopsy) include pain (15%), fever (3%), haematuria (20%), haematochezia (5%), and haemoejaculate (60%).

Prostate grade distribution

The grade of prostate cancer cases was reported in both the control and screening groups for the PLCO ('Table 2'), Norrkoping ('Table 3'), and ERSPC ('Table 4') studies. There were very limited data on metastatic disease.

Quality of life and cost of screening

None of the studies provided a complete assessment of the effect of screening on quality of life. Both the ERSPC and PLCO studies are currently assessing measures relating to quality of life. Authors from the ERSPC have published quality of life effects based on two participating sites in the study, which were modelled on the presence and absence of annual screening over the lifetime of 1000 men aged between 55 and 69 years (Heijnsdijk 2012). The model predicted a total of 73 life-years gained, with a relative increase of 40% of prostate cancer diagnoses, and relative decrease of 28% of prostate cancer deaths; with harms including 247 additional negative biopsies and 41 additional men receiving treatment. The number of quality-adjusted life-years (QALYs) gained was 56 (range -21 to 97). Results relating to quality of life from both studies are expected to be published upon completion of the analysis and will be included in future updates of this review. None of the included studies provided a comprehensive assessment of resource utilization associated with screening for prostate cancer. However, estimates on the cost-effectiveness of PSA screening from data extrapolated from the ERSPC study have been published (Shteynshlyuger 2011). Estimates from an earlier ERSPC publication reported that 1410 men would need to be screened (with the number of biopsies needed being 413 and subsequent number needed to treat of 48) to prevent one death from prostate cancer. Based on these figures, it has been estimated that it would cost between USD 262,758 and USD 347,549 per life-year saved (Shteynshlyuger 2011), which is not indicative of cost-effective care or high-value care even if overall mortality was reduced to the same magnitude as prostate cancer-specific mortality, an assumption that is unlikely.

DISCUSSION

Summary of main results

A total of five studies were included in this review. The studies differed considerably in their design, screening methodologies, frequencies, thresholds, and analysis, thus limiting the value of strict reliance on pooled estimates. We therefore provide an overview of the individual studies and an overall assessment of their results and potential patterns of findings. Based on evidence from five RCTs, prostate cancer screening that included PSA testing increased the number of men diagnosed with prostate cancer but did not reduce prostate cancer-specific or overall mortality. Findings from a 'core' subgroup enrolled in the ERSPC study indicated a 21% relative reduction in prostate cancer-specific mortality among men aged 55 to 69 years. The absolute effect was 1 per 936 screened and was not observed in other studies of men this age nor in other men enrolled in the ERSPC study. The relative reduction in risk was observed in two of the seven trials that participated in the ERSPC study, which had large effects that may have driven the findings. When performing a meta-analysis on the only two studies that were assessed to have 'low' risk of bias (ERSPC; PLCO), there was no significant difference in prostate cancer-specific mortality observed (RR 0.94, 95% CI 0.65 to 1.35). Screening led to diagnostic procedure-related harms that were generally minor but included pain, infection, and bleeding.

The ERSPC study consisted of seven sites that varied in the selection of participants with respect to age and length of follow-up. Differences were also apparent in the screening intervention. Sites differed in their use of the PSA test, DRE, and TRUS biopsies; either as standalone tests, or in combination. PSA cut-off values for biopsy also varied (ranging from 2.5 ng/mL to 4.0 ng/mL), along with the number of core biopsies. Screening interval differed between the sites, ranging from every two years, every four years, or between four to seven years. On average, each participant in the ‘core age group’ had 2.27 screening tests. Previous publications of the ERSPC study have reported a benefit for screening for a 'core' group of men. In updated publications, statistically significant results are not only in a 'core' group of men aged 55 to 69 years but are also present when all men that were randomised were evaluated for prostate cancer-specific mortality (RR 0.84, 95% CI 0.73 to 0.95) (ERSPC). It should be noted that the variations in the screening and follow-up methodologies employed across the eight participating sites (although results from the French site were not included in this analysis due to short duration of follow-up) may influence the results. During the 11-year median follow-up duration, it was estimated that a total of 1055 men would need to be invited to undergo screening, and 37 prostate cancers detected, in order to prevent one death from prostate cancer (ERSPC). Quality of life effects were modelled on two participating sites in the study, which calculated that the number of QALYs gained was 56 (range -21 to 97). The authors concluded that any benefit of screening was diminished by the loss of QALYs due to post-diagnosis effects including overdiagnosis. The QALY data should be interpreted with caution as the modelling was based on annual screening, whilst the ERSPC study sites used a variety of screening intervals (two years +).

The Norrkoping study did not provide a comparison of socio-demographic data between the screening and control groups. It also reported that information regarding the study was distributed through newspaper, radio, and television broadcasting. This raises the potential for contamination and self-selection bias, with participants in the control group choosing to be screened for prostate cancer. Furthermore, the quasi-random method of allocation, lack of allocation concealment, and potentially incomplete outcome data for men who migrated increase the risk of bias of the trial. This study failed to demonstrate a reduction in prostate cancer-specific mortality due to screening (RR 1.16, 95% CI 0.79 to 1.72).

The PLCO study was conducted at 10 sites across the USA. The methodological approach was uniform across all sites, with men aged 55 to 74 years recruited for the trial and the screening group offered annual DRE and PSA testing (with the cut-off being 4 ng/mL). Participants in the screening group were offered annual PSA testing for six years and annual DRE for four years. Totals of 85%

and 86% of men randomised to the screening group complied with the screening protocol for PSA testing and DRE, respectively, whereas 52% of men assigned to the control group underwent screening. The PLCO study reports on 10- and 13-year follow-up of participants; however, for the purposes of this review, the 10-year data were abstracted since this captures follow-up of 92% of participants compared to 57% at 13 years. With the exception of the analyses regarding tumour stage, which incorporated data from the 13-year follow up, all other analyses including the PLCO study utilised the 10-year follow-up data. Findings from this study did not identify a significant reduction in prostate cancer-specific mortality (RR 1.15, 95% CI 0.86 to 1.54), with results at 10 years of follow-up indicating no statistically significant increase in prostate cancer-specific mortality among screened individuals. While the high crossover rate is of concern in the PLCO study, the detection of prostate cancer in the screening group was 12% higher relative to the control group and the RRs for prostate cancer-specific mortality remained greater than 1.0 (that is higher in the screened versus the control group) even at 10 years after randomisation. These facts argue against crossover being a major reason why the PLCO study did not find a reduction in prostate cancer-specific mortality due to screening.

The Quebec study was limited by the lack of adherence to screening from participants randomised to the screening group. Although 31,133 men were randomised to receive screening for prostate cancer, only 23.6% of participants in this group actually complied with the randomisation and were screened. Similarly, approximately 7% of men randomised to the control group were screened for prostate cancer. Therefore, crossover between groups was an issue in this pragmatic trial. Data analysis was compromised as mortality data were not analysed according to the intention-to-screen principle. The authors of the trial reported a reduction in prostate cancer-specific mortality by comparing mortality in men who were screened to that of men who were not screened, regardless of their initial randomisation. Conversely, our analysis of the data, according to the intention-to-screen principle, showed no significant difference in mortality between the two groups (RR 1.01, 95% CI 0.76 to 1.33).

The Stockholm study allocated 2374 men to be screened, whilst 24,772 served as controls (that is not invited for screening). Men assigned to be screened received a one-time combination of DRE, PSA test, and TRUS biopsy. A PSA greater than 10.0 ng/mL was deemed the cut-off for biopsy, with repeat TRUS performed for PSA greater than 7.0 ng/mL. This study did not identify a significant reduction in prostate cancer-specific mortality (RR 1.09, 95% CI 0.83 to 1.45). Only three cancers were detected after repeat TRUS or after biopsies following increased PSA. Thus, this study is likely to have low applicability to current clinical practice.

Overall, reductions in prostate cancer-specific and overall mortality were not observed. Four of the five included studies in this review reported no significant benefit of screening for prostate cancer when all men that were randomised were analysed. Meta-analysis of eligible studies indicated no significant reduction in prostate cancer-specific mortality, regardless of whether men were screened from 45, 50, or 55 years of age. Both the whole randomised population and the subgroup of men aged 55 to 69 years that were enrolled in the ERSPC were found to have a significant decrease in prostate cancer-specific mortality following screening. Furthermore, even if assuming an actual overall benefit based on only the findings reported from the ERSPC (while ignoring the other RCT findings), the absolute magnitude of benefit is small, takes many years to accrue, and is accompanied by considerable overdetection. Any potential benefit of screening needs to be balanced with known harms associated with screening and with subsequent treatment. Several reports have quantified that the risks of screening and follow-up biopsy, while typically transient, are not infrequent and include pain, bleeding, and infection. For any benefit of screening to occur, treatment must be effective. While the SPCG-4 study demonstrated a reduction in prostate cancer-specific mortality and morbidity among men with prostate cancer detected primarily by methods other than PSA testing, the magnitude of benefit for mortality was about 5% and was confined to men aged < 65 years (Bill-Axelson 2008). Furthermore, several studies have reported on treatment-related morbidity that includes urinary, bowel, and sexual dysfunction (Johansen 2008; Wilt 2008a).

A meta-analysis of eligible studies indicated that screening was associated with an increase in the number of men diagnosed with prostate cancer (RR 1.30, 95% CI 1.02 to 1.65). Similarly, the proportion of localised prostate cancer was significantly greater in the screening group, with the proportion of advanced prostate cancer significantly higher in the control group. Despite this difference, a significant decrease in mortality was not demonstrated. Significant heterogeneity was associated with meta-analysis of these outcomes, which may be attributed to the varying PSA test cut-off levels, contamination in the control groups, or follow-up biopsy procedures across the various included studies. There were very limited data on metastatic disease, quality of life, or cost-effectiveness; however, a single quality of life derived model based on the ERSPC study suggests, at best, a small improvement in QALY that is not cost-effective.

Overall completeness and applicability of evidence

There were several gaps in the reporting of criteria required for assessing the risk of bias of studies. Authors of studies with information gaps were contacted. Additional information about methodological details was obtained from authors of the ERSPC, PLCO, and Norrkoping studies. Both the Quebec and Stockholm studies provided insufficient information to determine how sequence generation was performed. The Quebec study additionally did not provide clear information about how blinding of outcome assessment was achieved. The Norrkoping study provided incomplete data about withdrawals from the study.

Three of the studies were performed across European countries, whilst the remaining two were performed in North America. None of the studies were conducted in Asian, African, or other low-to-middle income countries.

Quality of the evidence

The quality of the evidence was assessed using the approach outlined in 'Characteristics of included studies'. The body of evidence was classified as high, unclear, or low risk of bias for each outcome. Risk of bias was assessed as high for the majority of outcomes, as only the ERSPC and PLCO studies were assessed to have a low risk of bias. Additionally, the GRADE framework was applied to rate the quality of the evidence, which was assessed as 'moderate' for mortality.

Potential biases in the review process

This review primarily consisted of published data. Unpublished data on all-cause mortality were obtained from the PLCO study. Future updated versions of the review will include more detailed analysis on primary and secondary outcomes as they become available through the continuing publications of the included studies.

Agreements and disagreements with other studies or reviews

The U.S. Preventive Services Task Force published an updated recommendation statement on screening for prostate cancer in 2012 (USPSTF 2012). The U.S. Preventive Services Task Force recommended against PSA-based screening (grade D recommendation). This clinical guideline based its recommendation largely on data from the PLCO and ERSPC studies as well as a comprehensive review of the evidence examining the potential benefits and harms of prostate cancer screening.

The European Association of Urology (EAU) 2012 Clinical Practice Guidelines have included information from the ERSPC, PLCO, and Quebec studies (EAU 2012; Heidenreich 2011). The EAU guidelines suggest that a baseline PSA determination at age 40 years might be beneficial for risk-stratification of patients, upon which further follow-up intervals can then be based. It states that a screening interval of eight years may be sufficient in men with a baseline PSA of 1 ng/mL or less. The statement concludes that PSA testing is not recommended in men older than 75 years.

The American Cancer Society practice guidelines, published in 2010, recommend that asymptomatic men who have at least a 10-year life expectancy should make an informed decision with their healthcare provider about screening for prostate cancer after they receive information about the uncertainties, risks, and potential benefits associated with prostate cancer screening. Men at average risk should receive this information beginning at age 50 years, whilst men in higher risk groups should receive this information before age 50 years (ACS 2010). This guideline included updated data from the ERSPC and PLCO studies, but not the Stockholm study.

The National Screening Committee in the United Kingdom (UK) has incorporated data from the ERSPC and PLCO studies (Burford 2010). It states that there are significant gaps in knowledge about the PSA test, prostate cancer, and treatment options. The National Screening Committee does not recommend a prostate cancer screening programme in the UK.

The Japanese Guideline for Prostate Cancer Screening, published in 2009, did not recommend population-based screening for prostate cancer. It also recommended that individual patients requesting screening be given appropriate information about the benefits and limitations of screening to assist their choice. Their recommendations only included preliminary data from the ERSPC study and did not include data from the Stockholm or PLCO studies (Hamashima 2009). The Japanese Urological Association recommends PSA screening for men at risk of prostate cancer. This guideline, published in 2010, includes data from the ERSPC and PLCO studies (JUA 2010).

The American Urological Association (AUA) published their Best Practice Statement in 2009 recommending that, given the uncertainty, patients need to be informed of the risks and benefits of testing for prostate cancer (AUA 2009). The AUA also recommends PSA screening only for well-informed patients who wish to pursue early diagnosis. This guideline incorporated results from the ERSPC and PLCO studies but not the Stockholm study.

The Royal Australian College of General Practitioners (RACGP) includes data from the ERSPC and PLCO studies but not the Stockholm study, and also cites the Djulbegovic 2010 systematic review and meta-analysis and the 2010 version of this review in their guidelines for preventive activities in general practice (RACGP 2012). The RACGP does not recommend routine screening for prostate cancer with DRE, PSA test, or transabdominal ultrasound. Rather, the RACGP concludes that patients should make their own decisions about being tested for prostate cancer after being fully informed of the potential benefits, risks, and uncertainties of prostate cancer testing.

Several systematic reviews have been published. As previously mentioned, a 2010 review by Djulbegovic concluded that there was no evidence to support routine use of screening for prostate cancer (Djulbegovic 2010). A 2012 systematic review also reported that screening demonstrated no significant benefit on reducing prostate cancer-specific mortality (Lumen 2012).

AUTHORS' CONCLUSIONS

Implications for practice

A pooled meta-analysis of the five included studies in this review identified that screening does not significantly decrease prostate cancer-specific mortality and is associated with a high degree of overdiagnosis, treatment and screening-related harms. Given the variation in study design and quality across the five included studies, it could be argued that pooling studies is not appropriate. However, assessment of four of the five studies individually using intention-to-screen analysis also indicated no decrease in prostate cancer-specific mortality. The only exception was the ERSPC study, which reported, in a pre-specified subgroup of men, that 1055 men needed to be invited to screening and 37 additional men subsequently diagnosed with prostate cancer needed to receive early intervention to prevent one additional prostate cancer death at a median follow-up duration of 11 years. The known harms associated with screening (false-positives with PSA testing, complications associated with TRUS-guided biopsies, overdiagnosis and treatment-related harms) suggest that any small mortality benefit of screening at 11 years would be challenged by the occurrence of these harms that occur early and may persist.

For men who express an interest in prostate cancer testing, including those with risk factors such as family history of prostate cancer and African ethnicity, clinicians should adopt a shared, informed approach to decision-making. Men should be informed of the lack of benefit to at least 10 years, and demonstrated adverse effects, when deciding whether or not to undertake screening for prostate cancer. Any benefits from prostate cancer screening may take up to 10 years to accrue (Bill-Axelson 2005; Bill-Axelson 2008; Bill-Axelson 2011; Johansson 2009). Men who have an anticipated life expectancy less than 10 to 15 years (either due to age or co-morbid conditions) should be informed that testing for prostate cancer is unlikely to be beneficial given harms associated with testing.

It should be noted that the available evidence from randomised trials summarised in this review is largely based on men of European descent. In the United States, black men appear to have a higher incidence and higher risk of dying from prostate cancer that is approximately twice that of other men (Howlader 2012); the reasons for this are unknown. Only 4% of men in the PLCO trial were non-Hispanic black men and, although no specific information is available, it can be assumed that few men in the ERSPC trial were non-white. Therefore, there is uncertainty about the benefits and harms of prostate cancer screening in black men and men with a family history of prostate cancer.

Several fundamental issues must be addressed when considering screening for prostate cancer. Screening for prostate cancer is primarily performed using the DRE and PSA test, yet the specificity and sensitivity of both of these modalities are not ideal (Holmström 2009). The consequences of heightened anxiety, further examinations through biopsies, and the considerable side effects associated with various prostate cancer treatments must be appreciated. This predicament is further compounded by the inability to understand whether identified neoplasms are clinically significant. Some slow growing tumours may never threaten a man's life, as is represented by the discrepancy between the incidence and deaths attributed to prostate cancer (Parkin 2005).

A number of principles have been proposed, including the burden of the disease and the effectiveness of diagnostic tests and treatments, to assess whether a screening program is successful (WHO 1968). Prostate cancer is accepted as an important health problem; however, uncertainty exists over the effectiveness of diagnostic tests and treatments available. Much debate exists about use of the PSA test and the implications of potential false-positive and false-negative results. Similarly, although various treatments for prostate cancer are available (for example watchful waiting, radical prostatectomy, hormone and radiotherapy), high quality evidence is still developing (Bill-Axelson 2008; Bill-Axelson 2011; Wilt 2012). In future years, findings from the current screening RCTs will shed further light on longer-term outcomes from screening for prostate cancer and will document quality of life outcomes. However, until such data is available greater emphasis will be placed on patient and doctor communication. Many medical organisations currently support the concept of patient-informed, shared decision-making, regardless of whether they support or reject screening for prostate cancer. In the absence of definitive evidence from RCTs, a shared approach to decision-making between doctors and patients should be encouraged for men who inquire about prostate cancer screening or who have previously undergone prostate cancer screening. Facilitating this process with the aid of appropriate patient education materials will promote informed patient choice (O'Connor 2009) while minimizing workload burden among primary care providers and permitting primary care clinicians to focus on other preventive healthcare strategies of proven effectiveness for other health conditions.

Prior to obtaining a PSA test, men should be informed about the known harms that are frequent, both in the immediate- and long-term, versus the potential for a benefit that may occur many years in the future. Clinicians may adopt either a 'reactive' or 'proactive' method of counselling patients on prostate cancer screening, depending on their attitudes to screening; that is clinicians in favour of screening men of a certain age will adopt a 'proactive' nature to counselling as opposed to those that wait for the patient to raise the topic of screening. We believe that rather than counselling all men (proactive), counselling should be targeted to men who ask about screening, or those who have previously screened, in order to provide updated information. This approach permits clinicians to focus time, effort, and resources on areas of greatest concern to their patients and where there is greatest evidence of effectiveness. Mass screening, selective and opportunistic screening in the absence of patient knowledge and consent should not be performed.

Implications for research

Findings from this review support further research across a variety of health disciplines. Further long-term follow-up from existing trials is required to gain a better understanding of the adverse events, quality of life, and economic impact of screening. A longer follow-up period of existing trials with respect to prostate cancer-specific mortality will also provide more robust evidence that can better inform any net benefit of screening for prostate cancer. Future research could incorporate time-to-event analysis to account for the longer duration of follow-up from the included trials. Any additional trials should aim to provide high quality data on the impact of prostate cancer screening on quality of life, potential harms, adverse events, and an economic evaluation in addition to mortality across different populations (for example Asia). Additionally, such studies should be conducted using appropriate, or justified, selection of participants, adequate allocation concealment, adequate blinding of assessors, completeness of follow-up, and analysis of data according to intention-to-screen principles when possible. Prostate cancer-specific mortality is also highly dependent on the effectiveness of treatment regimens. Greater research is required from long-term, high quality trials to inform the effectiveness of current treatment regimens including radical prostatectomy, radiotherapies and active surveillance.

Evidence suggests that the PSA test does not have the required characteristics to be used as a widespread screening test for prostate cancer (Holmström 2009). If the PSA test is to be used as a screening tool, greater evidence is needed to establish cut-off values for 'negative' and 'positive' test results to ensure that patients do not undergo unnecessary invasive investigations and, similarly, are able to be referred for further investigations when warranted. A systematic review of diagnostic test accuracy synthesising the current evidence would greatly inform the broader understanding of the PSA test, its characteristics and its value as a screening and diagnostic tool. Whilst the PSA test may be prostate-specific, it is not specific to prostate cancer. Therefore, continued research into alternative prostate-specific markers is required.

Additional research is also required to further identify the psychosocial aspect of screening, patient knowledge and uptake (or tendency for uptake) of screening, as well as clinician perspectives and needs on prostate cancer screening. Such research should include evidence-based strategies for communicating the evidence on the merits of prostate cancer screening to patients and clinicians given the current barriers to uptake of patient and clinician education on this issue.

ACKNOWLEDGEMENTS

We thank the referees and editors of the Prostatic Diseases and Urologic Cancers Group for their comments and valuable assistance.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ERSPC

Methods	The ERSPC program was a randomised, multi-centre trial across 9 European countries (The Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, Portugal, and France). Each country used different recruitment and randomisation procedures. Participants were randomised 1:1 in all sites apart from Finland, which undertook a 2:3 randomisation process. Length of follow-up was dependent on site of randomisation. The trial reports data on 8 countries (data from Portugal was not included in this follow-up period).
Participants	The core age group for male participants was 55 to 69 years. In Sweden, study investigators included men between the ages of 50 and 54 years, and investigators in the Netherlands, Italy, Belgium, and Spain included men up to the age of 74 years at entry. In Switzerland, men between the ages of 55 and 69 years were included, with screening up to the age of 75 years. In Finland, men were recruited at the ages of 55, 59, 63, and 67 years. Men with a diagnosis of prostate cancer were ineligible for the study. Numbers include: screening group - 112,569 (total) 72,891 ('core' age group); control group - 128,688 (total) 89,352 ('core' age group).
Interventions	Participants in the screening group were offered a combination of PSA testing, DRE and TRUS biopsy. Most sites used a PSA value of 3.0 ng/mL as the cut-off and indication for biopsy. In Finland, a PSA value of 4.0 ng/mL was used for cut-off - men with a value between 3.0 to 3.9 ng/mL underwent a DRE until 1998. In Italy, a PSA value of 4.0 ng/mL was the defined cut-off, but men with a PSA between 2.5 to 3.9 ng/mL underwent a DRE and TRUS. In the Belgian and Dutch sites, a combination of DRE, TRUS and PSA (with a cut-off of 4.0 ng/mL) was used until 1997 - from which PSA testing alone was used. In Belgium, the PSA cut-off value was 10.0 ng/mL initially. The screening interval at 6 of the 7 sites was 4 years - Sweden used a 2 year interval. There was a 7-year interval between 1st and 2nd screening rounds in Belgium.
Outcomes	Primary outcome was prostate cancer mortality. Also reported were all-cause mortality, number of prostate cancers diagnosed, clinical stage, Gleason score, and risk.

ERSPC *(Continued)*

Notes	A total of 82.2% of men in the screening group were screened at least once. The mean and median durations of follow-up were 10.5 and 11 years, respectively (core groups). No deaths were reported as a direct complication from the biopsy procedure. The rate of overdiagnosis in the screening group was estimated to be up to 50%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study was a multi-centre trial across 9 European countries that randomly assigned men to screening or control groups. "Within each country, men were assigned to either the screening group or the control group... on the basis of random number generators."
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in the publication. It was also unclear whether method of concealment differed among study sites given that different randomisation procedures were implemented across the different sites. "...randomization procedures differed among countries and were developed in accordance with national regulations."
Blinding (performance bias and detection bias) All outcomes	Low risk	It is not possible to blind participants and clinicians to the screening intervention. Causes of death were evaluated in a blinded manner. Causes of death were obtained from registries and individual chart reviews. A committee analysed causes of death at each centre, with an independent data and safety committee reviewing the trial. There was no information on blinding for other outcome measures (e.g. diagnosed cancers). "Causes of death were evaluated in a blinded fashion... or on the basis of official causes of death. The causes were classified by the independent committees."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data from the Portugal study centre were excluded from all analyses due to discontinuation. Data from the France centre of the trial were not included in mortality analyses due to short duration of follow-up, and were not included in primary analyses of additional outcomes - although data were provided. "the primary analysis was planned at the outset on the basis of follow-up of at least 10 years, which was reached with data through 2008. The current analyses include follow-up data through 2008…regarding the core age group analysis."
Selective reporting (reporting bias)	Low risk	Objectives of the ERSPC include cancer-specific mortality and quality of life outcomes. Mortality is reported but quality of life is not descriptively reported in this publication. Measures relating to quality of life are currently being reviewed and will form the basis of future publications. "…an evaluation of the effect on quality of life is pending."
Other bias	Unclear risk	Main data analysis is based on the core age group (55-69 years). There are differing age groups across the 8 reported sites. "The benefit of screening was restricted to the core age group of subjects who were between the ages of 55 and 69 years at the time of randomizations"

Norrkoping

Methods	Randomised controlled trial in Norrkoping, Sweden. Participants were men residing in the city of Norrkoping identified from a national population register. The study reports on a 20-year follow-up of participants on prostate cancer outcome.
Participants	Participants were male inhabitants of Norrkoping aged 50-69 years. Every sixth man was randomly allocated to the screening group from a list of dates of births obtained from the national population register. The remaining men served as controls. Only men 69 or younger were invited to the fourth screening round in 1996. There was no mention of any other specific exclusion criteria (e.g. previous diagnosis of prostate cancer or with symptoms). Numbers include: screening group - 1494; control group - 7532.
Interventions	Interventions were screening every three years versus control (not invited for screening). The first and second rounds of screening were performed only using a DRE. The first screening round DREs were performed by a general practitioner and a urologist. In the second and subsequent rounds, the DRE was performed by a general practitioner only. The third and fourth rounds of screening included a DRE and a PSA test. TRUS biopsy was performed if the DRE was deemed abnormal or if PSA was greater than 4.0 ng/mL.
Outcomes	Primary outcome was prostate cancer mortality at 20 years follow-up. Also reported were all-cause mortality, clinical stage and choice of therapy in men diagnosed with prostate cancer across both screened and control groups, and number of prostate cancers diagnosed.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Men were randomised to the screening group from a list of dates of birth. "... men were randomly allocated to be screened by including every sixth man from a list of dates of birth."
Allocation concealment (selection bias)	High risk	There was no description of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	It is not possible to blind participants and clinicians to the screening intervention. Prostate cancer mortality was obtained from a national cancer registry and cross-referenced against patient notes. There is no clear description of blinding during outcome assessment, however the outcomes (mortality, diagnosis) are unlikely to be influenced by lack of blinding. "In September 2009 cause of death was registered in a blinded review of the patients' records for all men who died."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals were cited, but it is unclear how the data for those men who migrated were available. There were no missing data for mortality, but some for number of men diagnosed, due to migration and death. "The screened cohort diminished from 1492 men at the start of the study to 1118 in 1996 due to migration and death."
Selective reporting (reporting bias)	Low risk	Outcomes presented in publications correlate to study protocol obtained from the authors.
Other bias	Low risk	Data presented to allow analysis according to intention-to-screen principle.

Norrkoping *(Continued)*

	"All analyses were performed based on intention to screen comparisons."

PLCO

Methods	The PLCO study was a randomised controlled trial across 10 study centres in the United States of America (USA). Each study centre used recruitment sources and strategies appropriate to the local situation. Participants were randomised 1:1. The study reports on a 10- to 13-year follow-up of participants regarding prostate cancer outcome.
Participants	Participants were males aged 55 to 74 years. Men with a history of prostate, lung or colorectal cancer were excluded, along with participants currently receiving cancer treatment except non-melanoma skin cancer. In 1995, men who had undertaken more than one PSA blood test in the previous three years were also excluded. Numbers include: screening group - 38,340; control group - 38,345.
Interventions	Participants in the screening group were offered annual PSA testing for six years and annual DRE for four years. A PSA value of 4.0 ng/mL was determined to be positive for prostate cancer. DREs were performed by physicians, qualified nurses or physician assistants. Men with positive PSA results, or abnormal DRE, were advised to seek diagnostic evaluation. Both participants and health-care providers received the results, and they decided upon the method of evaluating abnormal screening results.
Outcomes	Primary outcome was prostate cancer mortality at 10 years (92% follow up) and 13 years (57% follow up). Also reported were number of prostate cancers diagnosed, clinical stage and Gleason scores.
Notes	All-cause data provided in the trial report does not include deaths from prostate, lung, or colorectal (PLC) cancers – therefore not truly 'all-cause'. Authors were contacted, and updated information on all-cause mortality data inclusive of deaths from PLC cancers was provided for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Individual randomisation was performed within blocks stratified according to centre, age and sex. Atlhough the method used to generate allocation sequence was not mentioned in the trial report, it was provided in an earlier publication (PLCO - Prorock). "The randomization scheme uses blocks of random permutations of varying lengths and is stratified by SC (study centre), gender and age. Random assignment is implemented using compiled software and encrypted files loaded on SC microcomputers."
Allocation concealment (selection bias)	Low risk	Concealment was achieved through a central system. "As each person is successfully randomized into the trial, data including name, gender, date of birth and study arm are automatically stored in encrypted data tables."
Blinding (performance bias and detection bias) All outcomes	Low risk	It is not possible to blind participants and clinicians to the screening intervention. Data on diagnosed cancers and mortality were obtained by patient reported questionnaire and followed up by telephone (unblinded). This data was supplemented by linkage to the National Death Index. Death certificates were obtained to confirm deaths and determine cause. Possible cancer-specific deaths were reviewed by blinded reviewers.

PLCO *(Continued)*

		"Reviewers of these deaths were unaware of study-group assignments for deceased subjects."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on mortality and diagnosis are available for the 10-year follow up, but follow-up data on 13-year outcomes are not complete. "As of December 31, 2009 (the cutoff date for this analysis), the vital status of 92% of the trial participants was known at 10 years and of 57% of the participants at 13 years."
Selective reporting (reporting bias)	Low risk	Study protocol is available and the study's pre-specified outcomes have been reported. Outcomes, such as harms, are to be reported in future publications. "...there is evidence of harms, in part associated with the false-positive tests, but also with the overdiagnosis inseparable from PSA screening, especially in older men."
Other bias	High risk	Data were analysed according to the intention-to-screen principle. Data on contamination were also provided (estimated to be 40-52%).

Quebec

Methods	Randomised controlled trial in Quebec, Canada. Participants were men identified from electoral rolls and allocated 2:1 in favour of screening. The study reports on an 11-year follow-up of participants on prostate cancer outcome.
Participants	Participants were male inhabitants of Quebec city aged 45 to 80 years. Men with a previous diagnosis of prostate cancer or previously screened and referred to the study clinic for consultation were not eligible. Numbers include: screening group - 31,133; control group - 15,353.
Interventions	Interventions were annual screening versus control (not invited for screening). The first screening round included a PSA test and a DRE. TRUS biopsy was performed in cases with PSA > 3.0 ng/mL and/or abnormal DRE (except for first 1002 men who had all three procedures performed). Follow-up screening rounds included a PSA test. TRUS biopsy was only performed if PSA was above 3.0 ng/mL for the first time or increased by more than 20% from last measurement.
Outcomes	Primary outcome was prostate cancer mortality at 11 years follow-up. Also reported were prostate cancer death incidence rates in screened versus unscreened cohorts, and clinical stage and choice of therapy in men diagnosed with prostate cancer.
Notes	Crossover and contamination were issues for this pragmatic trial. The compliance and contamination rate within both the screening and control groups was described. From a total of 31,133 men randomised to the screening group, 7348 (23.6%) were actually screened (i.e. all 31,133 men were invited to be screened, but only 23.6% took up the invitation and actually were screened). Similarly, of the 15,353 randomised to the control group, 1122 (7.3%) were screened for prostate cancer at the study site. There was no report of any other withdrawals or whether participants in the control group were screened somewhere other than the study site; hence it is possible that more than 7.3% of the control group were actually screened. The data were re-analysed by the authors of this review according to the intention-to-screen principle.

Risk of bias

Bias	Authors' judgement	Support for judgement

Quebec *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No sequence generation process is mentioned. Authors only state that men were randomly assigned to groups. "... men were randomly allocated either to the group invited for annual screening or to the control group not invited for screening at a ratio of 2:1 in favor of screening."
Allocation concealment (selection bias)	High risk	No mention of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	It is not possible to blind participants and clinicians to the screening intervention. Blinding of outcome assessment was not clearly described. "The information on cause-specific death was obtained from the Death Registry of the Health Department of the Province of Quebec."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals from both the screening and control groups were cited.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	High risk	Data were not analysed according to the intention-to-screen principle. A total of 31,133 men were randomised to receive screening for prostate cancer, but only 23.6% of participants in this group actually complied with the randomisation and were screened. Similarly, approximately 7% of men randomised to the control group were screened for prostate cancer. "... all screened men were compared to all unscreened men irrespective of the original randomization group."

Stockholm

Methods	Randomised controlled trial in Stockholm, Sweden. Male participants living in the catchment area of Stockholm South Hospital were identified through census records. The study reports on a 15-year follow-up of participants on prostate cancer outcome.
Participants	Participants were all men aged between 55 to 70 years living in the catchment area of Stockholm South Hospital. Men with an earlier diagnosis of prostate cancer were excluded from the study. Numbers include: screening group - 2374; control group - 24,772.
Interventions	Inverventions were one-time screening versus control (not invited for screening). The screening consisted of DRE, PSA test and TRUS. TRUS-guided biopsies were performed if abnormal findings occurred during the DRE and/or TRUS. A repeat TRUS was performed if the PSA was greater than 7 ng/mL. Randomized quadrant biopsies were taken if the PSA was greater than 10 ng/mL.
Outcomes	Primary outcome was prostate cancer mortality at 15 years follow-up. Also reported was "any" cause mortality (including attendees and non-attendees), "other" cause mortality (including attendees and non-attendees), and number of prostate cancers diagnosed.
Notes	Median follow-up time was 12.9 years overall. Mean years follow up for the screened group was 12.9 years (0.2 to 15.7). Mean years follow up for the control group was 13.0 years (0.7 to 15.7).

Stockholm *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors only state that patients were randomly selected for screening. No additional information is provided on the method of randomisation. "... 2,400 (men) were randomly selected and invited to participate in a prostate cancer screening study...The 24,202 remaining men served as a control group."
Allocation concealment (selection bias)	High risk	No method of allocation concealment was described.
Blinding (performance bias and detection bias) All outcomes	Low risk	It is not possible to blind participants and clinicians to the screening intervention. There was no specific mention of blinding of outcome assessors. Outcomes (mortality and diagnosis) and outcome measurement are unlikely to be influenced by lack of blinding. Outcomes were obtained from a national cancer registry, with urologists independently reviewing medical records to assign cause of death. "We collected information on prostate cancer diagnosis and the date of diagnosis from the Swedish Cancer Register for the entire source population. From the Cause of Death register we collected information on date of death and the underlying cause of death... three senior urologists independently reviewed the medical records and assigned the cause of death."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data for mortality or number diagnosed. However, there was discrepancy between population sizes from Swedish census records in 1988 and Statistics Sweden records. "The file containing the registration number of the original 26,602 men...could not be retrieved due to a change of record holders. Therefore, we reconstructed the cohort...This comprised 27,204 men, that is, 602 (2%) more than in the original source population."
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Low risk	Data were analysed according to the intention-to-screen principle.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agalliu 2007	Case control study
Ahmed 2008	Cohort study - survey of a cohort of men regarding prostate screening awareness
Anonymous 2000	Descriptive study - report on a screening program in the USA
Anonymous 2008	Narrative review
Aus 2001	Cohort study - cancer detection rate via biopsy in men with an elevated PSA level in the screening group of the Swedish arm of the ERSPC

Study	Reason for exclusion
Aus 2004	Cohort study - explored the cumulative risk of cancer detection in a cohort of men from the screening group of the Swedish arm of the ERSPC
Aus 2005	Cohort study - reported the cumulative prostate cancer risk in men with different PSA levels within the Swedish arm of the ERSPC
Aus 2007	Preliminary results from the ERSPC
Auvinen 1996	Finnish pilot study for the ERSPC, with a 2 year follow-up and no results report for the control group
Auvinen 2009	Results from the ERSPC, but reported outcomes are not relevant to the systematic review
Bangma 1995a	Cohort study - evaluation of the diagnostic value of volume adjusted PSA values in a screening population of the Dutch feasibility study for the ERSPC
Bangma 1995b	Cohort study - explored the value of the f/t PSA ratio for cancer detection in the screening group of the Dutch arm of the ERSPC
Bangma 1995c	Cohort study - explored the value of the f/t PSA ratio, PSAD and PSA age references for cancer detection in the screening group of the Dutch arm of the ERSPC
Bangma 1997	Descriptive study - report on the design and features of the Dutch arm of the ERSPC
Beemsterboer 1999	Cohort study - explored the incidence of prostate cancer in the screening group of the Dutch arm of the ERSPC
Beemsterboer 2000	Survey - identified the rate of PSA testing before and during the Dutch arm of the ERSPC
Bergstralh 2007	Case control study
Boevee 2010	Results are available in the main article of ERSPC study
Borre 2007	Narrative review
Bul 2011	Results only from one arm of the ERSPC study
Bunker 2007	RCT - exploring lycopene supplementation for prostate cancer
Candas 2000	Cohort study - incidence of prostate cancer in screening cohort of the Quebec trial along with a cost assessment
Carlsson 2007	Study associated with the ERSPC study
Carlsson 2011	Results only from one arm of the ERSPC study
Carriere 2007	Ecological study
Chavarro 2008	Case control study
Ciatto 1993	Cohort study - Italian pilot feasibility study for the ERSPC with preliminary results
Ciatto 1994	Cohort study - Italian pilot feasibility study for the ERSPC with preliminary results

Study	Reason for exclusion
Ciatto 2002	Cohort study - analysis of PSA velocity in 'healthy' participants in the screening cohort within the Italian arm of the ERSPC
Ciatto 2003b	Descriptive study - report on the issue of screening within the control group of the Italian arm of the ERSPC
Ciatto 2008	Cohort study - relating to results from ERSPC
Collin 2008	Ecological study of prostate cancer mortality
Concato 2009	Narrative review
Cusan 1994	Descriptive study - report on the preliminary results of the Quebec trial
D'Amico 2007	RCT - exploring Finasteride for hair loss
de Koning 2002	Descriptive study - report on the preliminary results of the ERSPC and PLCO trials
Draisma 2009	Additional results from the ERSPC study, reporting on cancer lead time
Driscoll 2008	RCT - patient education trial
Döbrőssy 2007	Narrative review
Ellison 2008	RCT - study of patient education materials
Essink-Bot 1998	Cohort study - explored the health status of men randomised to screening in the Dutch arm of the ERSPC
Etzioni 2008	Narrative review
Fenton 2008	Cohort study - treatment of prostate cancer patients
Finne 2002	Cohort study - explored the diagnostic value of PSA properties in diagnosing prostate cancer in the screening group of the Finnish arm of the ERSPC
Finne 2010	Results from the ERSPC, but reported outcomes are not relevant to the systematic review
Fitzpatrick 2009	Narrative review
Fleshner 2007	Study protocol
Fleshner 2009	Narrative review
Ford 2003	Descriptive study - described the demographic details of the AAMEN project, which attempts to recruit African American men to the PLCO
Ford 2008	RCT - exploration of a case management intervention for prostate cancer patients
Frosch 2008	RCT - study exploring patient education materials
Gohagan 1994a	Descriptive study - report on the design of the PLCO
Gohagan 1994b	Editorial on the issue of screening for prostate cancer

Study	Reason for exclusion
Gohagan 1995	Descriptive study - report on the design of the PLCO
Gohagan 2000	Descriptive study - report on the design of the PLCO
Gonzalgo 2007	Narrative review
Gosselaar 2008	RCT - reporting associated findings from the ERSPC study
Gosselaar 2008b	Associated study within the ERSPC
Grosclaude 2008	Narrative review
Grubb 2008	RCT - preliminary results from the PLCO study
Grubb 2009	Cohort study - additional data relating to the PLCO study
Gustafsson 1992	Cohort study - explored the correlation between PSA measurement to prostate cancer in a randomly selected cohort of men screened for prostate cancer in Sweden
Gustafsson 1995	Cohort study - explored the cost effectiveness of prostate cancer screening in a randomly selected cohort of men in Sweden
Gustafsson 1998	Cohort study - explored the effectiveness of prostate cancer screening in a randomly selected cohort of men in Sweden
Heijnsdijk 2009	Results from the ERSPC, but reported outcomes are not relevant to the systematic review
Hoedemaeker 1999	Cohort study - explored the prostate cancer characteristics in a cohort of the screening group of the Dutch arm of the ERSPC
Hoedemaeker 2001	Cohort study - explored the frequency of PIN in prostate biopsies within the Dutch arm of the ERSPC
Horinaga 2007	Cohort study - diagnostic study
Hosseini 2007	Cohort study - mass screening of a cohort of men
Imamura 2008	Economic evaluation and review
Janes 2008	Cohort study - investigating epidemiological properties of screening
Jegu 2009	Results only from one arm of the ERSPC study
Johansen 2008	Cohort study - examination of hormone treatment and prostate cancer survival
Kawamura 2008	Cohort study - development of a nomogram for PSA testing
Kerfoot 2008	RCT - study of teaching materials
Kerfoot 2009	RCT - exploring patient education on prostate cancer screening
Kerkhof 2010	Results only from one arm of the ERSPC study
Kerns 2008	RCT - study of patient education materials

Study	Reason for exclusion
Khatami 2007	Preliminary results from the ERSPC study
Khatami 2009	Cohort study - exploring PSA doubling time
Kiemeny 2008	Cohort study - exploring family history of prostate cancer
Kilpeläinen 2010	Results only from one arm of the ERSPC study
Klotz 2008	Narrative review
Kramer 2009	Clinical guideline on prostate cancer treatment
Kramer 2009b	Clinical guideline on prostate cancer treatment
Kripalani 2007	RCT - exploring patient education materials
Krist 2007	RCT - exploring physician-patient discussion
Labrie 1992	Cohort study - explored the effectiveness of prostate cancer screening in a randomly selected cohort of men in Quebec, Canada
Labrie 1996	Cohort study - explored the stage and grade of prostate cancer in men within the screening arm of the Quebec study
Laurila 2010	Results are available in the main article of ERSPC study
Leitzmann 2008	Reports outcomes other than prostate cancer from the PLCO study
Leoni 2008	Cohort study - estimating measures of PSA testing
Lim 2008	Position statement
Lin 2006	Narrative review
Lin 2008	Guideline for prostate cancer screening
Lobel 2007	Narrative review
Lodding 1998	Cohort study - explored the biopsy characteristics in a cohort of the screening group from the Swedish arm of the ERSPC
Lucia 2008	Provided additional information for the PLCO study
Lujan 2004	Cohort study - explored the detection rates and clinical characteristics of cancers in a cohort of the screening group from the Spanish arm of the ERSPC
Makinen 2001	Cohort study - explored the detection rate in a cohort of the screening group from the Finnish arm of the ERSPC
Makinen 2002	Cohort study - explored the association between family history and diagnosis of prostate cancer in the screening group from the Finnish arm of the ERSPC
Makinen 2004	Cohort study - reported intermediate screening efficacy indicators within the Finnish arm of th ERSPC

Study	Reason for exclusion
Mao 2007	RCT - exploring prostate cancer treatments
Marcella 2008	Case control study
Meeks 2008	Cohort study - exploring PSA velocity
Mitterberger 2007	RCT - exploring ultrasound detection in prostate cancer patients
Määttänen 1999	Cohort study - explored the detection rate in a cohort of the screening group from the Finnish arm of the ERSPC
Määttänen 2001	Descriptive study - report on the preliminary results of the Finnish arm of the ERSPC
Määttänen 2007	Preliminary results of the ERSPC
Nanri 2007	Cohort study
Nelen 2010	Results from the ERSPC, but reported outcomes are not relevant to the systematic review
Norming 1991	Cohort study - explored the effectiveness of prostate cancer screening in a randomly selected cohort of men in Sweden
Otto 2003	ERSPC - explored the extent of opportunistic screening in the Dutch arm of the ERSPC
Otto 2010	Results are available in the main article of ERSPC study
Pedersen 1990	Cohort study - explored the effectiveness of prostate cancer screening in a randomly selected cohort of men in Sweden
Pienta 2009	A narrative review
Pinksy 2007	Associated study with the PLCO study
Pinsky 2010	Associated study with the PLCO study
Postma 2004	Cohort study - explored the incidence and circumstances of advanced prostate cancer in a cohort of the screening group from the Dutch arm of the ERSPC
Postma 2007	Preliminary results from the ERSPC
Prorok 1994	Descriptive study - report on the design of the PLCO
Raaijmakers 2004a	Cohort study - explored the cancer detection rate of men in a cohort from the screening group from the Dutch arm of the ERSPC
Raaijmakers 2004b	Cohort study - explored the indicators of prostate cancer from changes in PSA characteristics in a cohort from the screening group from the Dutch arm of the ERSPC
Raaijmakers 2007	Cohort study associated with the ERSPC
Rauscher 2008	Review
Recker 2001	Cohort study - explored the cancer detection rate of men in a cohort from the screening group from the Swiss arm of the ERSPC

Study	Reason for exclusion
Richard 2009	Commentary on the ERSPC study
Rietbergen 1997a	Cohort study - explored the cancer detection rates and characteristics within the screening group from the Dutch arm of the ERSPC
Rietbergen 1997b	Cohort study - explored the risk factors associated with performing a biopsy in a cohort of the screening group from the Dutch arm of the ERSPC
Rietbergen 1998a	Cohort study - explored the discriminating potential of the PSA test in a cohort of the screening group from the Dutch arm of the ERSPC
Rietbergen 1998b	Cohort study - explored the yield of serial screening in a cohort of the screening group from the Dutch arm of the ERSPC
Rietbergen 1999	Preliminary results of the ERSPC exploring the cancer detection rate and clinical features of men in the screening group from the Dutch arm of the ERSPC to the incidental cases in a region where no screening was performed
Roemeling 2007	Study associated with the ERSPC study
Roemeling 2007b	Study associated with the ERSPC study
Roemeling 2007c	Study associated with the ERSPC study
Romero 2008	Cohort study - exploring patient perception of DRE
Roobol 2004	Cohort study - explored possible predictors of prostate cancer in the screening group from the Dutch arm of the ERSPC
Roobol 2007	Study associated with the ERSPC study
Roobol 2007b	Study associated with the ERSPC study
Roobol 2009	Results from the ERSPC, but reported outcomes are not relevant to the systematic review
Rosser 2008	Editorial
Scattoni 2008	Descriptive study relating to ERSPC
Schröder 1995	Descriptive study - report on the pilot studies of the ERSPC
Schröder 1996	Dutch pilot studies to establish the feasibility of the ERSPC
Schröder 1997	Descriptive study - report on the design and features of the ERSPC
Schröder 1998	Cohort study - explored the value of the DRE as a stand alone test in the screening group from the Dutch arm of the ERSPC
Schröder 1999	Descriptive study - report on the design and features of the ERSPC
Schröder 2000	Cohort study - explored the diagnostic value of tests in a cohort of the screening group from the Dutch arm of the ERSPC
Schröder 2001a	Cohort study - explored the diagnostic value of tests in a cohort of the screening group from the Dutch arm of the ERSPC

Study	Reason for exclusion
Schröder 2001b	Descriptive study - commentary on the issue of screening for prostate cancer
Schröder 2005a	Cohort study - explored the PSA progression within a specified period of screened men
Schröder 2008	Interim findings of the ERSPC study
Schröder 2008b	Associated findings from the ERSPC study
Schröder 2009	Narrative review
Schröder 2009b	Reporting on a cohort of men from the ERSPC
Shteynshlyuger 2011	Study on cost-effectiveness related to PLCO - but does not provide results related to objectives of this systematic review
Sieverding 2008	Cohort study - survey results from a cohort of participants undergoing screening
Sotelo 2007	Cohort study - exploring assays for PSA testing
Stamatiou 2008	RCT - relating to patient education
Standaert 1997	Descriptive study - report on the progress of the ERSPC
Stephens 2008	Cohort study - exploring patient education on prostate cancer screening
Steyerberg 2007	Cohort study - exploring use of nomograms
Taha 2005	Cohort study - explored the effectiveness of prostate cancer screening in a randomly selected cohort of men in Saudi Arabia
Tarhan 2007	Cohort study - exploring PSA measurement
Thompson 2007	RCT - associated with the Prostate Cancer Prevention Trial
Thompson 2008	Cohort study - exploring the performance of PSA testing in the Prostate Cancer Prevention Trial
Thompson 2008b	Cohort study - exploring the effects of finasteride
Tornblom 2001	Cohort study - explored the correlation between PSA measurement to prostate cancer in a randomly selected cohort of men screened for prostate cancer in Sweden
Tornblom 2004	Cohort study - explored the lead time for prostate cancer detection in Sweden
Torres Zambrano 2007	Preliminary results from the ERSPC study
USPSTF 2008	Guideline and recommendation for prostate cancer screening
van den Bergh 2008	RCT - results from the Prostate Cancer Prevention Trial
van Leeuwen 2012	Results from the ERSPC, but reported outcomes are not relevant to the systematic review
van Weerden 2008	Narrative review
Varenhorst 1989	Cohort study - explored the effectiveness of prostate cancer screening in a randomly selected cohort of men in Sweden. Pilot results for the Norrkoping study. No data is given on the controls.

Study	Reason for exclusion
Varenhorst 1991	Cohort study - explored the effectiveness of prostate cancer screening in a randomly selected cohort of men in Sweden. Pilot results for the Norrkoping study. No data is given on the controls.
Verratti 2007	Cohort study
Vickers 2008	Cohort study - associated findings from the ERSPC study
Villers 2008	RCT - results from the Prostate Cancer Prevention Trial
Vis 2001a	Cohort study - explored the categorization of cancer in a select cohort of men from the screening group of the Dutch arm of the ERSPC
Vis 2001b	Cohort study - explored the value of differing screening protocols within the ERSPC
Vis 2002	Cohort study - explored the magnitude of prostate cancer detection by serendipity within the Dutch arm of the ERSPC
Vis 2007	Study associated with the ERSPC study
Wallner 2008	Cohort study - reporting psychosocial factors in screening
Weinrich 2007	RCT - exploring patient education materials
Weiss 2008	Case control study nested in the PLCO study
Wilbur 2008	Narrative review
Wilt 2008	Systematic review on five alpha reductase
Wolters 2008	Cohort study - additional information from the ERSPC study
Wolters 2010	Results from the ERSPC, but reported outcomes are not relevant to the systematic review
Yang 2008	Cohort study - exploring prostate cancer treatment
Yasunaga 2008	Cohort study - survey of men regarding screening issues
Zackrisson 2003	Cohort study - explored the value of serial screening in a cohort of the screening group from the Swedish arm of the ERSPC
Zackrisson 2004	Cohort study - explored the clinical and pathological cancer characteristics within the Swedish arm of the ERSPC
Zhu 2011	Results from the Rotterdam arm of the ERSPC

Characteristics of ongoing studies *[ordered by study ID]*

CAP

Trial name or title	Comparison Arm for ProtecT (CAP)
Methods	The CAP study cluster-randomised primary care (general practice) centres located in and around eight United Kingdom (UK) cities.

CAP *(Continued)*

Participants	Participants are men 50 to 69 years of age without diagnosed prostate cancer attending one of the over 550 cluster-randomised primary care centres. Estimated enrolment: Intervention arm – 225,000 men Comparison arm – 225,000 men
Interventions	Intervention group receives a single round of PSA testing (total PSA threshold ≥ 3.0 ng/mL) as part of the ProtecT study. Comparison group receives the UK National Health Service Prostate Cancer Risk Management advice.
Outcomes	Primary outcomes are "prostate cancer or intervention-related specific mortality at an average of 10 years following randomization." The study is also evaluating prostate cancer diagnosis, death, and clinical and resource use data.
Starting date	2002.
Contact information	J.A Lane (athene.lane@bristol.ac.uk).
Notes	"Findings for both trials (CAP and ProtecT) regarding prostate cancer-specific mortality will be published in around 2016."

DATA AND ANALYSES

Comparison 1. Screening versus control

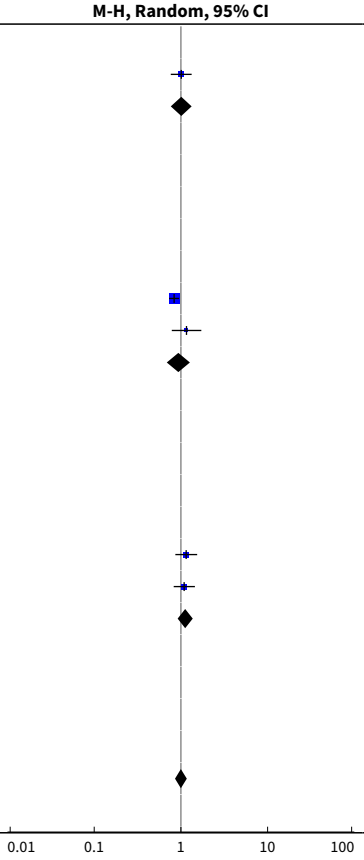
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prostate cancer-specific mortality (subgroup analysis age)	5	341342	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.17]
1.1 Men aged ≥ 45 years	1	46486	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.76, 1.33]
1.2 Men aged ≥ 50 years	2	191025	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.69, 1.27]
1.3 Men aged ≥ 55 years	2	103831	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.92, 1.37]
2 Prostate cancer-specific mortality (subgroup analysis age, including ERSPC 'core' age group)	5	321586	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.83, 1.19]
2.1 Men aged ≥ 45 years	1	46486	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.76, 1.33]
2.2 Men aged ≥ 50 years	1	9026	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.79, 1.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Men aged ≥ 55 years	3	266074	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.75, 1.27]
3 Prostate cancer-specific mortality (sensitivity analysis overall risk of bias)	2	258684	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.30]
3.1 Low risk of bias	2	258684	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.30]
4 Prostate cancer-specific mortality (sensitivity analysis overall risk of bias, including ERSPC 'core' age group)	2	238928	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.65, 1.35]
4.1 Low risk of bias	2	238928	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.65, 1.35]
5 All-cause mortality (subgroup analysis age)	4	294856	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.96, 1.03]
5.1 Men aged ≥ 50 years	2	191025	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.84, 1.56]
5.2 Men aged ≥ 55 years	2	103831	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]
6 All-cause mortality (subgroup analysis age, including ERSPC 'core' age group)	4	275100	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.96, 1.03]
6.1 Men aged ≥ 50 years	1	9026	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.06, 1.79]
6.2 Men aged ≥ 55 years	3	266074	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.97, 1.00]
7 All-cause mortality (sensitivity analysis overall risk of bias)	2	258684	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.96, 1.02]
7.1 Low risk of bias	2	258684	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.96, 1.02]
8 All-cause mortality (sensitivity analysis overall risk of bias, including ERSPC 'core' age group)	2	238928	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.97, 1.00]
8.1 Low risk of bias	2	238928	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.97, 1.00]
9 Prostate cancer diagnosis (subgroup analysis age)	4	294856	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.02, 1.65]
9.1 Men aged ≥ 50 years	2	191025	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.54, 1.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Men aged ≥ 55 years	2	103831	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.08, 1.17]
10 Prostate cancer diagnosis (subgroup analysis age, including ERSPC 'core' age group)	4	275100	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.03, 1.64]
10.1 Men aged ≥ 50 years	1	9026	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.16, 1.86]
10.2 Men aged ≥ 55 years	3	266074	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.96, 1.64]
11 Tumour stage (localised T1-T2, N0, M0)	3	247954	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.19, 2.70]
12 Tumour stage (advanced T3-4, N1, M1)	3	247954	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.73, 0.87]

Analysis 1.1. Comparison 1 Screening versus control, Outcome 1 Prostate cancer-specific mortality (subgroup analysis age).

Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Men aged ≥ 45 years					
Quebec	153/31133	75/15353		18.65%	1.01[0.76,1.33]
Subtotal (95% CI)	**31133**	**15353**		**18.65%**	**1.01[0.76,1.33]**
Total events: 153 (Screening), 75 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
1.1.2 Men aged ≥ 50 years					
ERSPC	364/82816	522/99183		33.9%	0.84[0.73,0.95]
Norrkoping	30/1494	130/7532		11.6%	1.16[0.79,1.72]
Subtotal (95% CI)	**84310**	**106715**		**45.5%**	**0.93[0.69,1.27]**
Total events: 394 (Screening), 652 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=2.45, df=1(P=0.12); I^2=59.2%					
Test for overall effect: Z=0.43(P=0.66)					
1.1.3 Men aged ≥ 55 years					
PLCO	98/38340	85/38345		17.53%	1.15[0.86,1.54]
Stockholm	53/2374	506/24772		18.32%	1.09[0.83,1.45]
Subtotal (95% CI)	**40714**	**63117**		**35.85%**	**1.12[0.92,1.37]**
Total events: 151 (Screening), 591 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%					
Test for overall effect: Z=1.12(P=0.26)					
Total (95% CI)	**156157**	**185185**		**100%**	**1[0.86,1.17]**
Total events: 698 (Screening), 1318 (Control)					



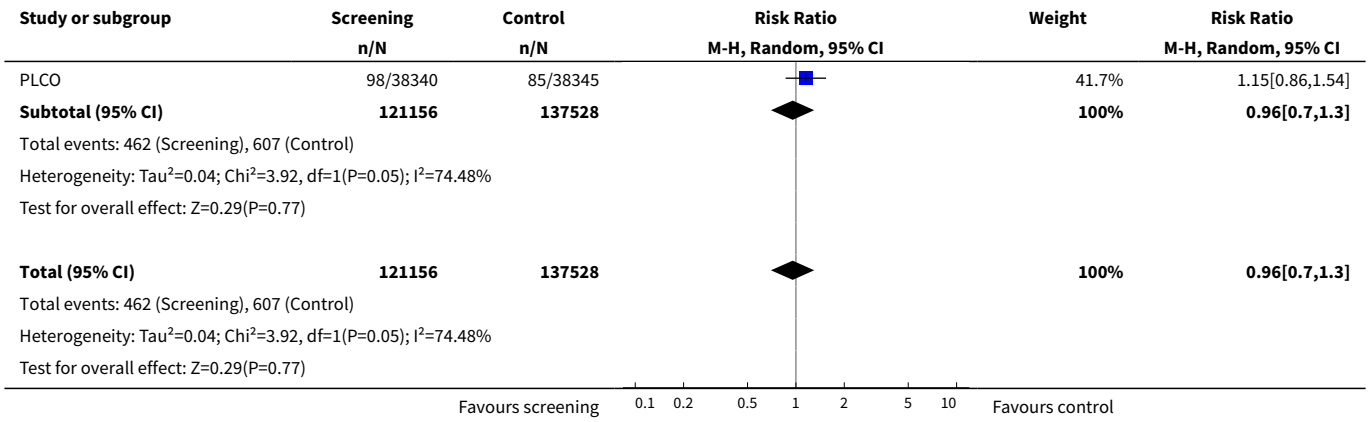
Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.01; Chi²=7.4, df=4(P=0.12); I²=45.95%					
Test for overall effect: Z=0.01(P=0.99)					
Test for subgroup differences: Chi²=1.06, df=1 (P=0.59), I²=0%					

Analysis 1.2. Comparison 1 Screening versus control, Outcome 2 Prostate cancer-specific mortality (subgroup analysis age, including ERSPC 'core' age group).

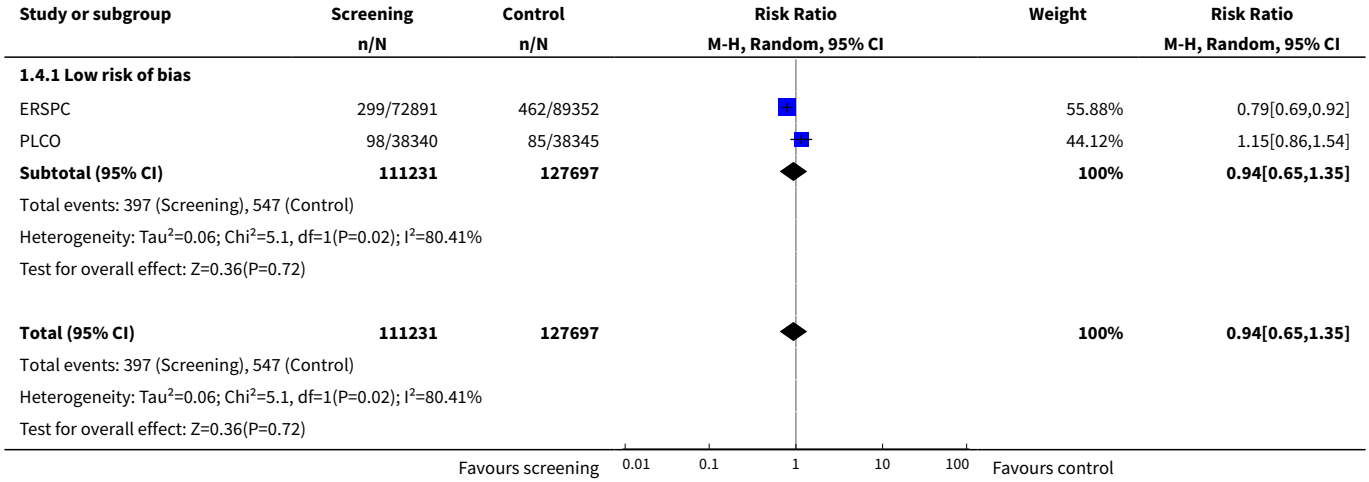
Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Men aged ≥ 45 years					
Quebec	153/31133	75/15353		19.57%	1.01[0.76,1.33]
Subtotal (95% CI)	**31133**	**15353**		**19.57%**	**1.01[0.76,1.33]**
Total events: 153 (Screening), 75 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
1.2.2 Men aged ≥ 50 years					
Norrkoping	30/1494	130/7532		13.28%	1.16[0.79,1.72]
Subtotal (95% CI)	**1494**	**7532**		**13.28%**	**1.16[0.79,1.72]**
Total events: 30 (Screening), 130 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
1.2.3 Men aged ≥ 55 years					
ERSPC	299/72891	462/89352		29.22%	0.79[0.69,0.92]
PLCO	98/38340	85/38345		18.64%	1.15[0.86,1.54]
Stockholm	53/2374	506/24772		19.29%	1.09[0.83,1.45]
Subtotal (95% CI)	**113605**	**152469**		**67.15%**	**0.98[0.75,1.27]**
Total events: 450 (Screening), 1053 (Control)					
Heterogeneity: Tau²=0.04; Chi²=7.54, df=2(P=0.02); I²=73.48%					
Test for overall effect: Z=0.18(P=0.86)					
Total (95% CI)	**146232**	**175354**		**100%**	**1[0.83,1.19]**
Total events: 633 (Screening), 1258 (Control)					
Heterogeneity: Tau²=0.02; Chi²=9.55, df=4(P=0.05); I²=58.11%					
Test for overall effect: Z=0.03(P=0.98)					
Test for subgroup differences: Chi²=0.55, df=1 (P=0.76), I²=0%					

Analysis 1.3. Comparison 1 Screening versus control, Outcome 3 Prostate cancer-specific mortality (sensitivity analysis overall risk of bias).

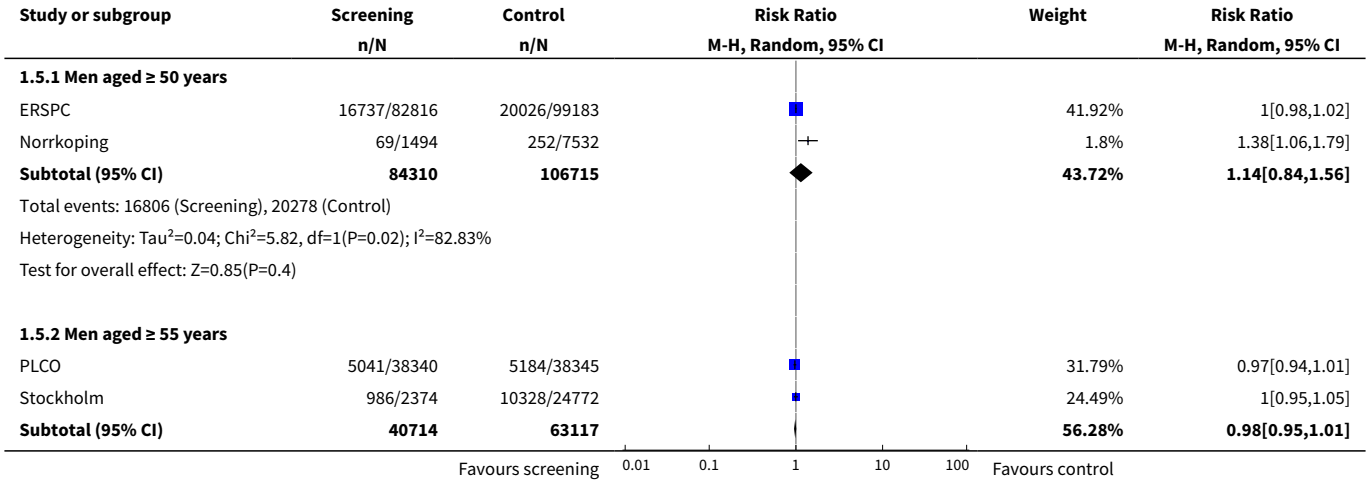
Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Low risk of bias					
ERSPC	364/82816	522/99183		58.3%	0.84[0.73,0.95]



Analysis 1.4. Comparison 1 Screening versus control, Outcome 4 Prostate cancer-specific mortality (sensitivity analysis overall risk of bias, including ERSPC 'core' age group).



Analysis 1.5. Comparison 1 Screening versus control, Outcome 5 All-cause mortality (subgroup analysis age).



Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 6027 (Screening), 15512 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.6, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=1.31(P=0.19)					
Total (95% CI)	**125024**	**169832**		**100%**	**1[0.96,1.03]**
Total events: 22833 (Screening), 35790 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.99, df=3(P=0.05); I^2=62.44%					
Test for overall effect: Z=0.2(P=0.84)					
Test for subgroup differences: Chi^2=0.94, df=1 (P=0.33), I^2=0%					

Favours screening 0.01 0.1 1 10 100 Favours control

Analysis 1.6. Comparison 1 Screening versus control, Outcome 6 All-cause mortality (subgroup analysis age, including ERSPC 'core' age group).

Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Men aged ≥ 50 years					
Norrkoping	69/1494	252/7532		1.66%	1.38[1.06,1.79]
Subtotal (95% CI)	**1494**	**7532**		**1.66%**	**1.38[1.06,1.79]**
Total events: 69 (Screening), 252 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.43(P=0.02)					
1.6.2 Men aged ≥ 55 years					
ERSPC	13917/72891	17256/89352		42.37%	0.99[0.97,1.01]
PLCO	5041/38340	5184/38345		31.92%	0.97[0.94,1.01]
Stockholm	986/2374	10328/24772		24.06%	1[0.95,1.05]
Subtotal (95% CI)	**113605**	**152469**		**98.34%**	**0.99[0.97,1]**
Total events: 19944 (Screening), 32768 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.79, df=2(P=0.67); I^2=0%					
Test for overall effect: Z=1.66(P=0.1)					
Total (95% CI)	**115099**	**160001**		**100%**	**0.99[0.96,1.03]**
Total events: 20013 (Screening), 33020 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.17, df=3(P=0.07); I^2=58.18%					
Test for overall effect: Z=0.53(P=0.59)					
Test for subgroup differences: Chi^2=6.38, df=1 (P=0.01), I^2=84.33%					

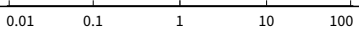
Favours screening 0.01 0.1 1 10 100 Favours control

Analysis 1.7. Comparison 1 Screening versus control, Outcome 7 All-cause mortality (sensitivity analysis overall risk of bias).

Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Low risk of bias					
ERSPC	16737/82816	20026/99183		65.17%	1[0.98,1.02]
PLCO	5041/38340	5184/38345		34.83%	0.97[0.94,1.01]

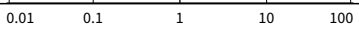
Favours screening 0.01 0.1 1 10 100 Favours control

Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**121156**	**137528**		**100%**	**0.99[0.96,1.02]**
Total events: 21778 (Screening), 25210 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.94, df=1(P=0.16); I^2=48.54%					
Test for overall effect: Z=0.66(P=0.51)					
Total (95% CI)	**121156**	**137528**		**100%**	**0.99[0.96,1.02]**
Total events: 21778 (Screening), 25210 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.94, df=1(P=0.16); I^2=48.54%					
Test for overall effect: Z=0.66(P=0.51)					



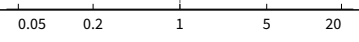
Analysis 1.8. Comparison 1 Screening versus control, Outcome 8 All-cause mortality (sensitivity analysis overall risk of bias, including ERSPC 'core' age group).

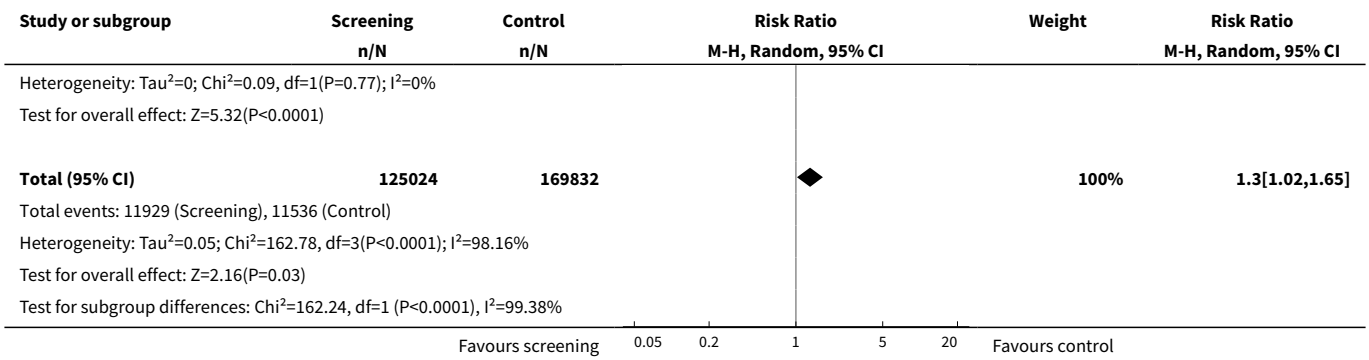
Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Low risk of bias					
ERSPC	13917/72891	17256/89352		76.38%	0.99[0.97,1.01]
PLCO	5041/38340	5184/38345		23.62%	0.97[0.94,1.01]
Subtotal (95% CI)	**111231**	**127697**		**100%**	**0.98[0.97,1]**
Total events: 18958 (Screening), 22440 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=1.71(P=0.09)					
Total (95% CI)	**111231**	**127697**		**100%**	**0.98[0.97,1]**
Total events: 18958 (Screening), 22440 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=1.71(P=0.09)					



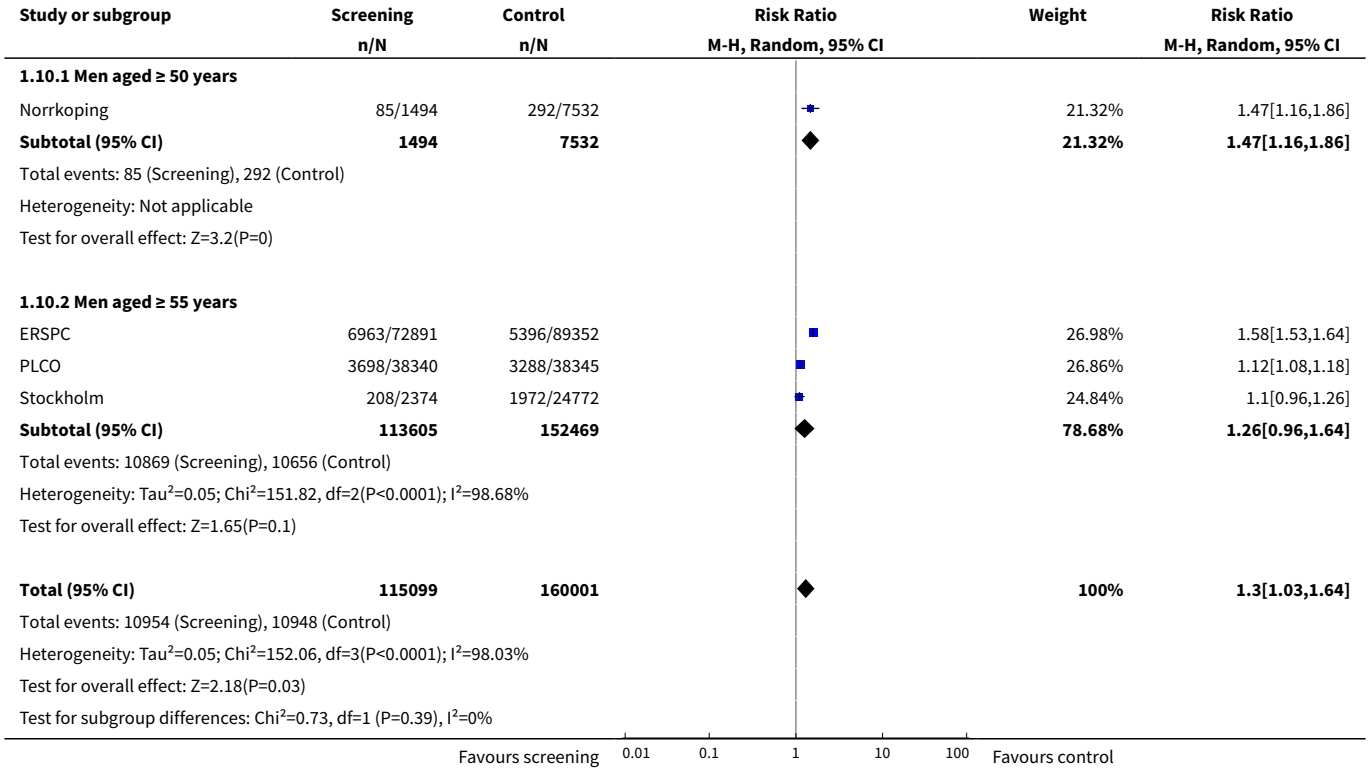
Analysis 1.9. Comparison 1 Screening versus control, Outcome 9 Prostate cancer diagnosis (subgroup analysis age).

Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Men aged ≥ 50 years					
ERSPC	7938/82816	5984/99183		26.93%	1.59[1.54,1.64]
Norrkoping	85/1494	292/7532		21.41%	1.47[1.16,1.86]
Subtotal (95% CI)	**84310**	**106715**		**48.34%**	**1.59[1.54,1.64]**
Total events: 8023 (Screening), 6276 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.43, df=1(P=0.51); I^2=0%					
Test for overall effect: Z=28.3(P<0.0001)					
1.9.2 Men aged ≥ 55 years					
PLCO	3698/38340	3288/38345		26.81%	1.12[1.08,1.18]
Stockholm	208/2374	1972/24772		24.85%	1.1[0.96,1.26]
Subtotal (95% CI)	**40714**	**63117**		**51.66%**	**1.12[1.08,1.17]**
Total events: 3906 (Screening), 5260 (Control)					

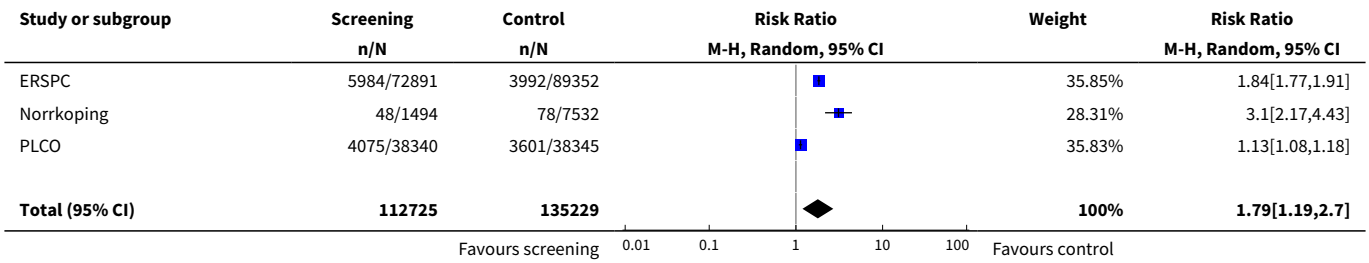


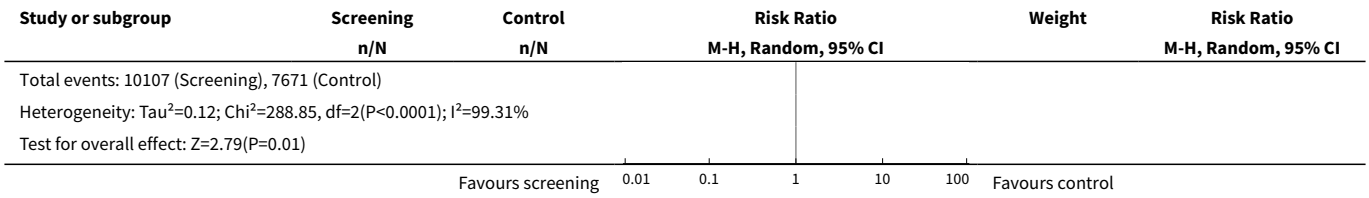


Analysis 1.10. Comparison 1 Screening versus control, Outcome 10 Prostate cancer diagnosis (subgroup analysis age, including ERSPC 'core' age group).

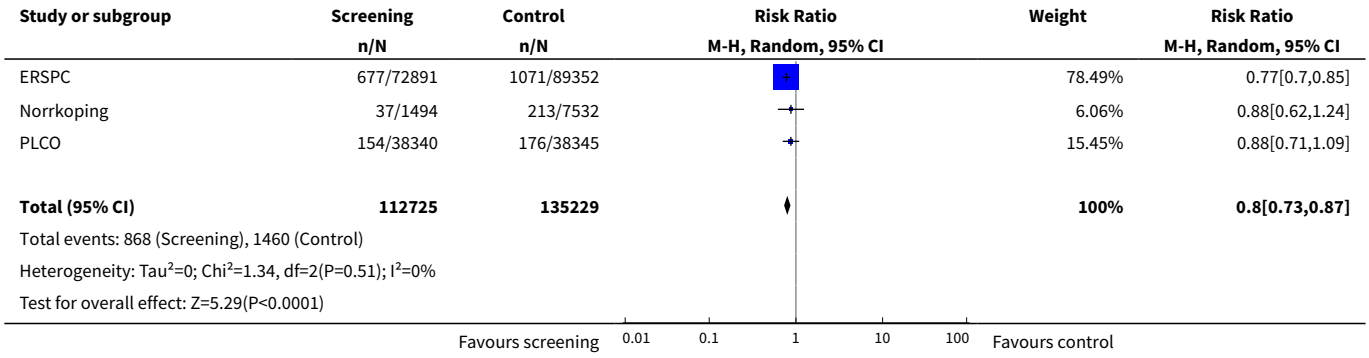


Analysis 1.11. Comparison 1 Screening versus control, Outcome 11 Tumour stage (localised T1-T2, N0, M0).





Analysis 1.12. Comparison 1 Screening versus control, Outcome 12 Tumour stage (advanced T3-4, N1, M1).



ADDITIONAL TABLES

Table 1. Stage of prostate cancer in the screening group (Quebec)

Clinical stage	Number of men (%) at 1st visit	Number of men (%) at follow up
A2	1 (0.4)	0
A3	2 (0.8)	0
B0	15 (6.4)	21 (17.9)
B1	86 (36.4)	63 (53.9)
B2	69 (29.2)	22 (18.8)
C1	28 (11.9)	10 (8.5)
C2	20 (8.5)	1 (0.8)
D1	3 (1.3)	0
D2	12 (5.1)	0
N/A	8	6
Total	244	123

Table 2. Prostate tumour grade (PLCO)

Tumour Grade	Number of men (%) in control	Number of men (%) in screened
G2-4	137 (4.6)	222 (6.4)
G5-6	1,656 (55.0)	2,047 (58.9)
G7	779 (25.9)	815 (23.4)
G8-10	377 (12.5)	315 (9.1)
Unknown	61 (2.0)	79 (2.3)
Total	3,010	3,478

Table 3. Prostate tumour grade (Norrkoping)

Tumour Grade	# (%) in control	# (%) in screened
G1	94 (32.2)	43 (50.6)
G2	149 (51.0)	31 (36.5)
G3	43 (14.7)	11 (12.9)
GX/tumour grade not recorded	6 (2.1)	0 (0)
Total	292	85

Table 4. Prostate tumour grade (ERSPC)

Tumour Grade	# (%) in control	# (%) in screened
G2-6	2,564 (47.5)	4,528 (65.0)
G7	1,488 (27.6)	1,433 (20.6)
G>7	857 (15.9)	574 (8.2)
GX/tumour grade not recorded	487 (9.0)	428 (6.2)
Total	5,396	6,963

APPENDICES

Appendix 1. Electronic database search strategy

The following search strategy was used for MEDLINE, PROSTATE register and CANCERLIT:

1. Prostate-Specific Antigen/
2. prostate specific antigen.mp
3. psa.mp.
4. digital rectal examination.mp.
5. dre.mp.
6. transrectal ultrasound$.mp.
7. TRUS.mp.
8. or/1-7
9. Mass Screening/
10. screening.mp
11. or/9-10
12. Prostatic Neoplasms/pc, di [Prevention & Control, Diagnosis]
13. prostat$ cancer.mp
14. or/12-13
15. clinical trial.pt.
16. random$.mp
17. ((single or double) adj (Blind$ or mask$)).mp
18. placebo$.mp
19. or/14-18
20. 8 and 11 and 14 and 19

The following search strategy was used for EMBASE:

1. Prostate-Specific Antigen/
2. prostate specific antigen.mp
3. psa.mp.
4. digital rectal examination.mp.
5. dre.mp.
6. transrectal ultrasound$.mp.
7. TRUS.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Mass Screening/
10. screening.mp
11. 9 or 10
12. Prostate Tumor/pc, di [Prevention, Diagnosis]
13. prostat$ cancer.mp
14. 12 or 13
15. clinical trial.pt.
16. random$.mp
17. ((single or double) adj (Blind$ or mask$)).mp
18. placebo$.mp
19. or/14-18
20. 8 and 11 and 14 and 19

The following search strategy was used for the Cochrane Central Register of Controlled Trials (CENTRAL) and the NHS EED:

1. PROSTATE-SPECIFIC ANTIGEN
2. (prostate next specific next antigen)
3. psa
4. (digital next rectal next examination)
5. dre
6. (transrectal next ultrasound*)
7. trus
8. (#1 or #2 or #3 or #4 or #5 or #6 or #7)

9. MASS SCREENING
10.screening
11.(#9 or #10)
12.PROSTATIC NEOPLASMS
13.(prostat* next cancer)
14.(#12 or #13)
15.(#8 and #11 and #14)

WHAT'S NEW

Date	Event	Description
20 November 2012	New search has been performed	The review was updated to include a June 2012 search for published and unpublished studies. New outcomes data were abstracted from three studies and incorporated in the meta-analysis. This update was completed with revised authorship.
20 November 2012	New citation required but conclusions have not changed	The review was updated and the conclusions did not change.

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 3, 2006

Date	Event	Description
22 September 2010	Amended	Under 'electronic searches' we changed the sentence " An updated search of the electronic databases was performed with the existing search strategy on the 10 June, 2009" to " An updated search of the electronic databases was performed with the existing search strategy in July 2010."
10 June 2009	New search has been performed	Search strategy re-run and review updated.

CONTRIBUTIONS OF AUTHORS

Dragan Ilic initiated the review and wrote the initial protocol. He conducted the literature search, reviewed abstracts and full-text studies for inclusion, performed quality assessment, data extraction, analysis, and writing of the review.

Molly M Neuberger performed data extraction, quality assessment, analysis, and reviewed the full-text of the review.

Mia Djulbegovic contributed to the literature search, reviewed abstracts for inclusion, performed data extraction and quality assessment.

Philipp Dahm co-initiated the review update, reviewed abstracts and full-text studies for inclusion, performed quality assessment, and contributed to the writing of the review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Department of Urology, College of Medicine, University of Florida, USA.
- Malcom Randall Veterans Affairs Medical Center, Gainesville, Florida, USA.

External sources

- Dennis W. Jahnigen Career Development Scholars Award by the American Geriatrics Society, USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Assessment for study risk of bias has been performed using the Cochrane Collaboration's risk-of-bias tool in this review. The GRADE framework has been applied in this review to assess the quality of the evidence as reported in the summary of findings table.

INDEX TERMS

Medical Subject Headings (MeSH)

Biopsy, Fine-Needle [adverse effects]; Digital Rectal Examination [*methods]; Endoscopic Ultrasound-Guided Fine Needle Aspiration [methods]; Mass Screening [*methods] [statistics & numerical data]; Prostate [pathology]; Prostate-Specific Antigen [*blood]; Prostatic Neoplasms [*diagnosis] [*mortality]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Aged, 80 and over; Humans; Male; Middle Aged